

3rd Edition



HARRISON'STM

CARDIOVASCULAR MEDICINE

JOSEPH LOSCALZO

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CARDIOVASCULAR
MEDICINE

Derived from Harrison's Principles of Internal Medicine, 19th Edition

Editors

DENNIS L. KASPER, md

William Ellery Channing Professor of Medicine, Professor of Microbiology and Immunobiology, Department of Microbiology and Immunobiology, Harvard Medical School; Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts

ANTHONY S. FAUCI, md

Chief, Laboratory of Immunoregulation; Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

STEPHEN L. HAUSER, md

Robert A. Fishman Distinguished Professor and Chairman, Department of Neurology, University of California, San Francisco, San Francisco, California

DAN L. LONGO, md

Professor of Medicine, Harvard Medical School; Senior Physician, Brigham and Women's Hospital; Deputy Editor, New England Journal of Medicine, Boston, Massachusetts

J. LARRY JAMESON, md, phd

Robert G. Dunlop Professor of Medicine; Dean, Perelman School of Medicine at the University of Pennsylvania; Executive Vice-President, University of Pennsylvania for the Health System, Philadelphia, Pennsylvania

JOSEPH L. OSCALZO, md, phd

Hersey Professor of the Theory and Practice of Medicine, Harvard Medical School; Chairman, Department of Medicine, and Physician-in-Chief, Brigham and Women's Hospital, Boston, Massachusetts

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EDITOR

Joseph Loscalzo, MD PhD

Hersey Professor of the Theory and Practice of Medicine,
Harvard Medical School; Chairman, Department of Medicine;
Physician-in-Chief, Brigham and Women's Hospital
Boston, Massachusetts



New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

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CONTRIBUTORS

Numbers in brackets refer to the chapter(s) written or cowritten by the contributor.

Jamil Aboulhosn, MD

Assistant Professor of Medicine; Director Ahmanson/UCLA Adult Congenital Heart Disease Center, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California [22]

Elliott M. Antman, MD

Professor of Medicine, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital; Associate Dean for Clinical/Translational Research, Harvard Medical School, Boston, Massachusetts [39, 41]

Eric H. Awtry, MD

Cardiology Division, Boston Medical Center, Boston, Massachusetts [29, 30]

Robert C. Basner, MD

Professor of Clinical Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York [Appendix]

Deepak L. Bhatt, MD, MPH

Professor of Medicine, Harvard Medical School; Chief of Cardiology, VA Boston Healthcare System; Senior Physician, Brigham and Women's Hospital; Senior Investigator, TIMI Study Group, Boston, Massachusetts [42]

Eugene Braunwald, MD, MA (Hon), ScD (Hon), FRCP

Distinguished Hersey Professor of Medicine, Harvard Medical School; Founding Chairman, TIMI Study Group, Brigham and Women's Hospital, Boston, Massachusetts [7, 28, 40]

Cynthia D. Brown, MD

Associate Professor of Clinical Medicine, Division of Pulmonary, Critical Care, Sleep and Occupational Medicine Indiana University, Indianapolis, Indiana [Review and Self-Assessment]

Christopher P. Cannon, MD

Professor of Medicine, Harvard Medical School; Senior Physician, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts [40]

Jonathan R. Carapetis, MBBS, PhD, FRACP, FAFPHM

Director, Telethon Kids Institute, The University of Western Australia, Crawley, Western Australia [32]

Agustin Castellanos, MD, FACC, FAHA

Professor of Medicine; Director, Clinical Electrophysiology, University of Miami Miller School of Medicine, Cardiovascular Division, Miami, Florida [35]

Murali Chakinala, MD

Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri [19]

John S. Child, MD, FACC, FAHA, FASE

Streisand Professor of Medicine and Cardiology; Director, Ahmanson-UCLA Adult Congenital Heart Disease Center; Director, UCLA Adult Noninvasive Cardiodiagnostics Laboratory Ronald Reagan-UCLA Medical Center, Geffen School of Medicine, University of California, Los Angeles (UCLA), Los Angeles, California [22]

Wilson S. Colucci, MD, FAHA, FACC

Thomas J. Ryan Professor of Medicine, Boston University School of Medicine; Chief of Cardiovascular Medicine, Boston Medical Center, Boston, Massachusetts [29, 30]

Mark A. Creager, MD

Professor of Medicine and Surgery, Director, Heart and Vascular Center, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Marcelo F. Di Carli, MD

Professor, Department of Radiology, Harvard Medical School; Chief, Division of Nuclear Medicine and Molecular Imaging; Executive Director, Noninvasive Cardiovascular Imaging Program, Brigham and Women's Hospital, Boston, Massachusetts [12, 51]

Robert H. Eckel, MD

Professor of Medicine, Division of Endocrinology, Metabolism and Diabetes, Division of Cardiology; Professor of Physiology and Biophysics, Charles A. Boettcher, II Chair in Atherosclerosis, University of Colorado School of Medicine, Anschutz Medical Campus, Director Lipid Clinic, University of Colorado Hospital, Aurora, Colorado [38]

Andrew J. Einstein, MD, PhD

Victoria and Esther Aboodi Assistant Professor of Medicine; Director, Cardiac CT Research; Co-Director, Cardiac CT and MRI, Department of Medicine, Cardiology Division, Department of Radiology, Columbia University College of Physicians and Surgeons, New York-Presbyterian Hospital, New York, New York [Appendix]

Jonathan A. Epstein, MD

William Wikoff Smith Professor; Chair, Department of Cell and Developmental Biology; Scientific Director, Penn Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania [1]

David P. Faxon, MD

Vice Chair of Medicine for Strategic Planning, Department of Medicine, Brigham and Women's Hospital; Senior Lecturer, Harvard Medical School, Boston, Massachusetts [13, 42, 53]

J. Michael Gaziano, MD, MPH

Professor of Medicine, Harvard Medical School; Chief, Division of Aging, Brigham and Women's Hospital; Director, Massachusetts Veterans Epidemiology Center, Boston VA Healthcare System, Boston, Massachusetts [2]

Thomas A. Gaziano, MD, MSc

Assistant Professor of Medicine, Harvard Medical School; Assistant Professor, Health Policy and Management, Center for Health Decision Sciences, Harvard School of Public Health; Faculty Co-Leader, Chronic and Cardiovascular Diseases Working Group, Harvard Institute for Global Health, Harvard University; Associate Physician in Cardiovascular Medicine, Department of Cardiology, Brigham and Women's Hospital, Boston, Massachusetts [2]

Ary L. Goldberger, MD

Professor of Medicine, Harvard Medical School; Wyss Institute for Biologically Inspired Engineering, Harvard University; Beth Israel Deaconess Medical Center, Boston, Massachusetts [11, 50, 52]

Samuel Z. Goldhaber, MD

Professor of Medicine, Harvard Medical School; Director, Thrombosis Research Group, Brigham and Women's Hospital, Boston, Massachusetts [45]

Helen H. Hobbs, MD

Professor, Internal Medicine and Molecular Genetics, University of Texas Southwestern Medical Center; Investigator, Howard Hughes Medical Institute, Dallas, Texas [37]

Judith S. Hochman, MD

Harold Snyder Family Professor of Cardiology, Clinical Chief, Leon Charney Division of Cardiology, Co-Director, NYU-HHC Clinical and Translational Science Institute; Director, Cardiovascular Clinical Research Center, New York University School of Medicine, New York, New York [34]

Brian Houston, MD

Division of Cardiology, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland [Review and Self-Assessment]

Sharon A. Hunt, MD, FACC

Professor of Medicine, Cardiovascular Medicine, Stanford University, Palo Alto, California [21]

David H. Ingbar, MD

Professor of Medicine, Pediatrics, and Physiology; Director, Pulmonary Allergy, Critical Care and Sleep Division, University of Minnesota School of Medicine, Minneapolis, Minnesota [34]

Roy M. John, MBBS, PhD, FRCP

Assistant Professor of Medicine, Harvard Medical School; Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts [18]

Adolf W. Karchmer, MD

Professor of Medicine, Harvard Medical School, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts [31]

Louis V. Kirchhof, MD, MPH

Professor, Departments of Internal Medicine (Infectious Diseases) and Epidemiology, University of Iowa; Staff Physician, Department of Veterans Affairs Medical Center, Iowa City, Iowa [33]

Theodore A. Kotchen, MD

Professor Emeritus, Department of Medicine; Associate Dean for Clinical Research, Medical College of Wisconsin, Milwaukee, Wisconsin [43]

Alexander Kratz, MD, MPH, PhD

Associate Professor of Clinical Pathology and Cell Biology, Columbia University College of Physicians and Surgeons; Director, Core Laboratory, Columbia University Medical Center and the New York Presbyterian Hospital; Director, the Allen Hospital Laboratory, New York, New York [Appendix]

Raymond Y. Kwong, MD, MPH

Associate Professor of Medicine, Harvard Medical School; Director of Cardiac Magnetic Resonance Imaging, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts [12, 51]

Neil K. Lakdawala, MD

Instructor in Medicine, Harvard Medical School; Associate Physician, Cardiovascular Medicine, Brigham and Women's Hospital; Boston VA Healthcare; Boston, Massachusetts [27]

Jane A. Leopold, MD

Associate Professor of Medicine, Harvard Medical School; Brigham and Women's Hospital, Boston, Massachusetts [13, 53]

Peter Libby, MD

Mallinckrodt Professor of Medicine, Harvard Medical School; Chief, Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts [1, 36]

Joseph Loscalzo, MD, PhD

Hersey Professor of the Theory and Practice of Medicine, Harvard Medical School; Chairman, Department of Medicine, and Physician-in-Chief, Brigham and Women's Hospital, Boston, Massachusetts [1, 3, 6–10, 23–27, 39, 41, 46–49]

Hari R. Mallidi, MD

Associate Professor of Surgery and Chief, Division of Transplant and Assist Devices; Lester and Sue Smith Endowed Chair in Surgery, Baylor College of Medicine, Houston, Texas [21]

Douglas L. Mann, MD

Lewin Chair and Chief, Cardiovascular Division; Professor of Medicine, Cell Biology and Physiology, Washington University School of Medicine, Cardiologist-in-Chief, Barnes Jewish Hospital, St. Louis, Missouri [19]

Mandeep R. Mehra, MD, FACC, FACP

Professor of Medicine, Harvard Medical School; Executive Director, Center for Advanced Heart Disease, Brigham and Women's Hospital; Co-Director, Brigham and Women's Hospital Heart and Vascular Center, Boston, Massachusetts [20]

Gregory F. Michaud, MD

Assistant Professor of Medicine, Harvard Medical School; Brigham and Women's Hospital, Boston, Massachusetts [17]

David A. Morrow, MD, MPH

Associate Professor of Medicine, Harvard Medical School; Director, Levine Cardiac Intensive Care Unit; Senior Investigator, TIMI Study Group, Brigham and Women's Hospital, Boston, Massachusetts [4]

Robert J. Myerburg, MD

Professor, Departments of Medicine and Physiology, Division of Cardiology; AHA Chair in Cardiovascular Research, University of Miami Miller School of Medicine, Miami, Florida Robert J. Myerburg [35]

Patrick T. O'Gara, MD

Professor of Medicine, Harvard Medical School; Director, Clinical Cardiology, Brigham and Women's Hospital, Boston, Massachusetts [9, 10, 23–26]

Michael A. Pesce, PhD

Professor Emeritus of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons; Director, Biochemical Genetics Laboratory, Columbia University Medical Center, New York Presbyterian Hospital, New York, New York [Appendix]

Daniel J. Rader, MD

Seymour Gray Professor of Molecular Medicine; Chair, Department of Genetics; Chief, Division of Translational Medicine and Human Genetics, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania [37]

Anis Rassi, Jr., MD, PhD, FACC, FACP, FAHA

Scientific Director, Anis Rassi Hospital, Goiânia, Brazil [33]

Richard M. Schwartzstein, MD

Ellen and Melvin Gordon Professor of Medicine and Medical Education, Harvard Medical School; Associate Division Chief, Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts [5]

Scott D. Solomon, MD

Professor, Harvard Medical School; Director, Noninvasive Cardiology, Brigham and Women's Hospital, Boston, Massachusetts [12, 51]

David D. Spragg, MD

Associate Professor, Department of Medicine, Johns Hopkins University; Director, Electrophysiology Laboratory, Johns Hopkins Bayview Medical Center, Baltimore, Maryland [14–16]

Lynne Warner Stevenson, MD

Professor of Medicine, Harvard Medical School; Director, Heart Failure Program, Brigham and Women's Hospital, Boston, Massachusetts [27]

William G. Stevenson, MD

Director, Clinical Cardiac Electrophysiology Program, Brigham and Women's Hospital; Cardiovascular Division, Department of Medicine, Harvard Medical School, Boston, Massachusetts [17, 18]

Stephen C. Textor, MD

Professor of Medicine, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota [44]

Gordon F. Tomaselli, MD

Michel Mirowski, MD Professor of Cardiology; Professor of Medicine and Cellular and Molecular Medicine; Chief, Division of Cardiology, Johns Hopkins University, Baltimore, Maryland [14–16]

Aaron B. Waxman, MD, PhD, FACP, FCCP

Associate Professor of Medicine, Harvard Medical School; Executive Director, Center for Pulmonary-Heart Diseases, Brigham and Women's Hospital Heart and Vascular Center, Boston, Massachusetts [49]

Charles M. Wiener, MD

Vice President of Academic Affairs, Johns Hopkins Medicine International, Professor of Medicine and Physiology, Johns Hopkins School of Medicine, Baltimore, Maryland [Review and Self-Assessment]

PREFACE

Harrison's Principles of Internal Medicine has been a respected information source for more than 60 years. Over time, the traditional textbook has evolved to meet the needs of internists, family physicians, nurses, and other health care providers. The growing list of Harrison's products now includes Harrison's for the iPad, Harrison's Manual of Medicine, and Harrison's Online. This book, Harrison's Cardiovascular Medicine, now in its third edition, is a compilation of chapters related to cardiovascular disorders.

Our readers consistently note the sophistication of the material in the specialty sections of Harrison's. Our goal was to bring this information to our audience in a more compact and usable form. We have also included a Review and Self-Assessment section that includes questions and answers to provoke reflection and to provide additional teaching points.

Cardiovascular disease is the leading cause of death in the United States accounting for one-quarter of all deaths annually, and is now also a major cause of death in the developing world. Advances in the therapy and prevention of cardiovascular diseases have clearly improved the lives of patients with these common, potentially devastating disorders; yet, the disease prevalence and the risk factor burden for disease (especially obesity in the United States and smoking worldwide) continue to increase globally. Cardiovascular medicine is, therefore, of crucial importance to the field of internal medicine.

Cardiovascular medicine is a large and growing subspecialty, and comprises a number of specific subfields, including coronary heart disease, congenital heart disease, valvular heart disease, cardiovascular imaging, electrophysiology, and interventional cardiology. Many of these areas involve novel technologies that facilitate diagnosis and therapy. The highly specialized nature of these disciplines within cardiology and the increasing specialization of cardiologists argue for the importance of a broad view of cardiovascular medicine by the internist in helping to guide the patient through illness and the decisions that arise in the course of its treatment.

The scientific underpinnings of cardiovascular medicine have also been evolving rapidly. The molecular pathogenesis and genetic basis for many diseases are now known and, with this knowledge, diagnostics and therapeutics are becoming increasingly individualized. Cardiovascular diseases are largely complex phenotypes, and this structural and physiological complexity recapitulates the complex molecular and genetic systems that underlie it. As knowledge about these complex systems expands, the opportunity for identifying unique therapeutic

targets increases, holding great promise for definitive interventions in the future.

In view of the importance of cardiovascular medicine to the field of internal medicine, and the rapidity with which the scientific basis for the discipline is advancing, Harrison's Cardiovascular Medicine was developed. The purpose of this sectional is to provide the readers with a succinct overview of the field of cardiovascular medicine. To achieve this goal, Harrison's Cardiovascular Medicine comprises the key cardiovascular chapters contained in the nineteenth edition of Harrison's Principles of Internal Medicine, contributed by leading experts in the field. This sectional is designed not only for physicians-in-training on cardiology rotations, but also for practicing clinicians, other health care professionals, and medical students who seek to enrich and update their knowledge of this rapidly changing field. The editors trust that this book will increase both the readers' knowledge of the field, and their appreciation for its importance.

The first section of the book, "Introduction to Cardiovascular Disorders," provides a systematic overview, beginning with the basic biology of the cardiovascular system, followed by epidemiology of cardiovascular disease, and approach to the patient. The integration of pathophysiology with clinical management is a hallmark of Harrison's, and can be found throughout each of the subsequent disease-oriented chapters. The book is divided into six main sections that reflect the scope of cardiovascular medicine: (I) Introduction to the Cardiovascular System; (II) Diagnosis of Cardiovascular Disorders; (III) Heart Rhythm Disturbances; (IV) Disorders of the Heart; (V) Disorders of the Vasculature; and (VI) Cardiovascular Atlases.

Our access to information through web-based journals and databases is remarkably efficient. Although these sources of information are invaluable, the daunting body of data creates an even greater need for synthesis by experts in the field. Thus, the preparation of these chapters is a special craft that requires the ability to distill core information from the ever-expanding knowledge base. The editors are, therefore, indebted to our authors, a group of internationally recognized authorities who are masters at providing a comprehensive overview while being able to distill a topic into a concise and interesting chapter. We are also indebted to our colleagues at McGraw-Hill. Jim Shanahan is a champion for Harrison's and these books were impeccably produced by Kim Davis. We hope you find this book useful in your effort to achieve continuous learning on behalf of your patients.

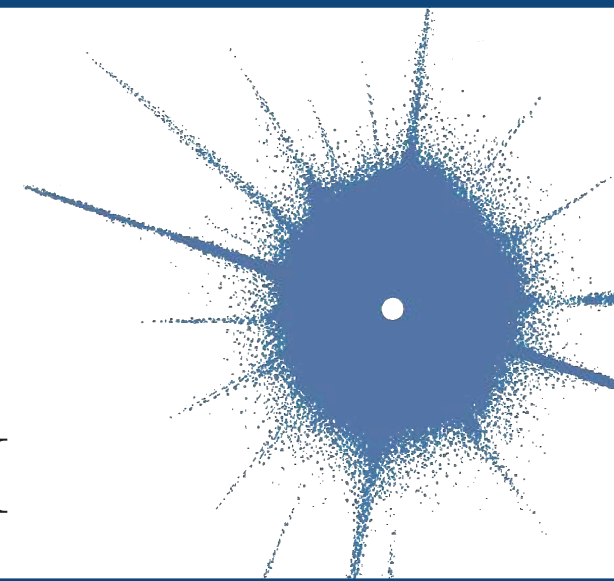
Joseph Loscalzo, MD, PhD

SECTION I

INTRODUCTION TO CARDIOVASCULAR DISORDERS

CHAPTER 1

BASIC BIOLOGY OF THE CARDIOVASCULAR SYSTEM



Joseph Loscalzo ■ Peter Libby ■ Jonathan A. Epstein

THE BLOOD VESSEL

VASCULAR ULTRASTRUCTURE

Blood vessels participate in homeostasis on a moment-to-moment basis and contribute to the pathophysiology of diseases of virtually every organ system. Hence, an understanding of the fundamentals of vascular biology furnishes a foundation for understanding the normal function of all organ systems and many diseases. The smallest blood vessels—capillaries—consist of a monolayer of endothelial cells apposed to a basement membrane, adjacent to occasional smooth-muscle-like cells known as pericytes (Fig. 1-1A). Unlike larger vessels, pericytes do not invest the entire microvessel to form a continuous sheath. Arteries typically have a trilaminar structure (Fig. 1-1B–E). The intima consists of a monolayer of endothelial cells continuous with those of the capillaries. The middle layer, or tunica media, consists of layers of smooth-muscle cells; in veins, the media can contain just a few layers of smooth-muscle cells (Fig. 1-1B). The outer layer, the adventitia, consists of looser extracellular matrix with occasional fibroblasts, mast cells, and nerve terminals. Larger arteries have their own vasculature, the vasa vasorum, which nourishes the outer aspects of the tunica media. The adventitia of many veins surpasses the intima in thickness.

The tone of muscular arterioles regulates blood pressure and flow through various arterial beds. These smaller arteries have a relatively thick tunica media in relation to the adventitia (Fig. 1-1C). Medium-size muscular arteries similarly contain a prominent tunica media (Fig. 1-1D); atherosclerosis commonly affects this type of muscular artery. The larger elastic arteries have a much more structured tunica media consisting of concentric bands of smooth-muscle cells, interspersed with strata of elastin-rich extracellular matrix sandwiched between layers of smooth-muscle cells (Fig. 1-1E). Larger arteries have a clearly demarcated internal elastic lamina that forms the barrier between the intima and

the media. An external elastic lamina demarcates the media of arteries from the surrounding adventitia.

ORIGIN OF VASCULAR CELLS

The intima in human arteries often contains occasional resident smooth-muscle cells beneath the monolayer of vascular endothelial cells. The embryonic origin of smooth-muscle cells in various types of artery differs. Some upper-body arterial smooth-muscle cells derive from the neural crest, whereas lower-body arteries generally recruit smooth-muscle cells from neighboring mesodermal structures during development. Derivatives of the proepicardial organ, which gives rise to the epicardial layer of the heart, contribute to the vascular smooth-muscle cells of the coronary arteries. Bone marrow–derived endothelial progenitors may aid repair of damaged or aging arteries. In addition, multipotent vascular stem cells resident in vessel walls may give rise to the smooth-muscle cells that accumulate in injured or atheromatous arteries.

VASCULAR CELL BIOLOGY

Endothelial cell

The key cell of the vascular intima, the endothelial cell, has manifold functions in health and disease. The endothelium forms the interface between tissues and the blood compartment. It therefore must regulate the entry of molecules and cells into tissues in a selective manner. The ability of endothelial cells to serve as a selectively permeable barrier fails in many vascular disorders, including atherosclerosis, hypertension, and renal disease. This dysregulation of permeability also occurs in pulmonary edema and other situations of “capillary leak.”

The endothelium also participates in the local regulation of blood flow and vascular caliber. Endogenous

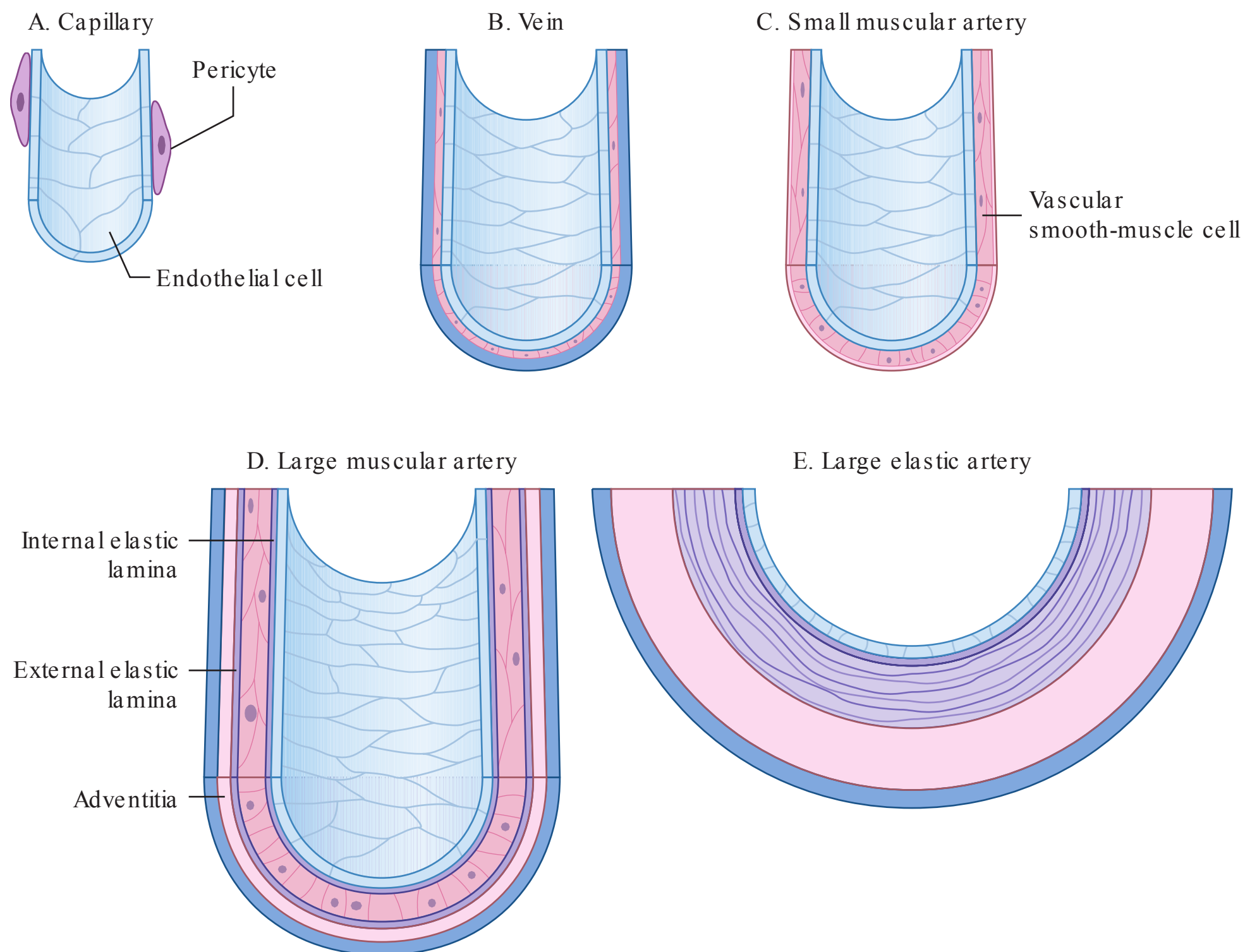


FIGURE 1-1

Schematics of the structures of various types of blood vessels. A. Capillaries consist of an endothelial tube in contact with a discontinuous population of pericytes. B. Veins typically have thin medias and thicker adventitias. C. A small muscular artery features a prominent tunica media. D. Larger muscular arteries have a prominent media with smooth-muscle cells embedded in a complex extracellular matrix. E. Larger elastic arteries have cylindrical layers of elastic tissue alternating with concentric rings of smooth-muscle cells.

substances produced by endothelial cells such as prostacyclin, endothelium-derived hyperpolarizing factor, nitric oxide (NO), and hydrogen peroxide (H_2O_2) provide tonic vasodilatory stimuli under physiologic conditions in vivo (**Table 1-1**). Impaired production or excess catabolism of NO impairs this endothelium-dependent vasodilator

function and may contribute to excessive vasoconstriction in various pathologic situations. Measurement of flow-mediated dilatation can assess endothelial vasodilator function in humans (**Fig. 1-2**). By contrast, endothelial cells also produce potent vasoconstrictor substances such as endothelin in a regulated fashion. Excessive

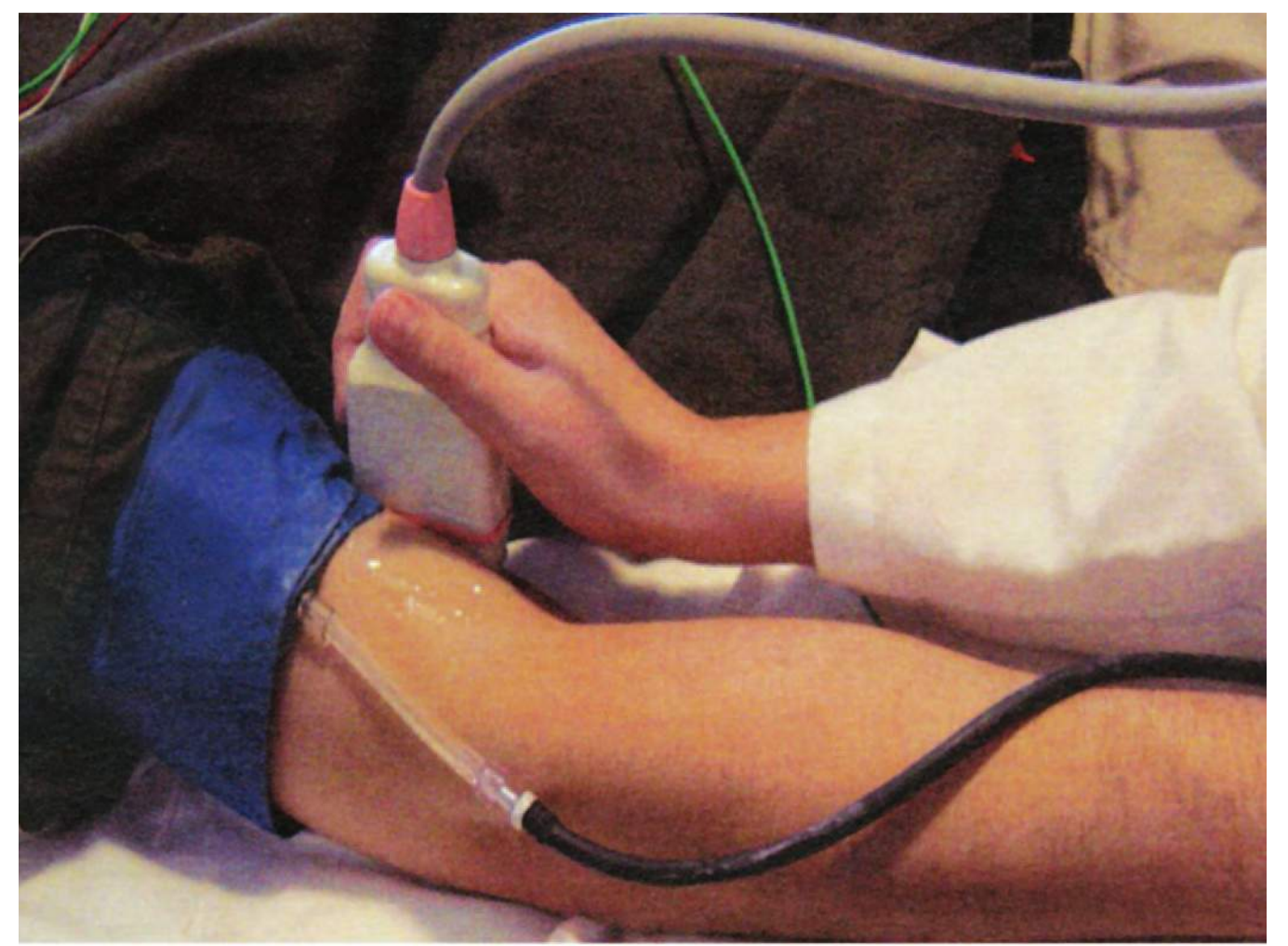
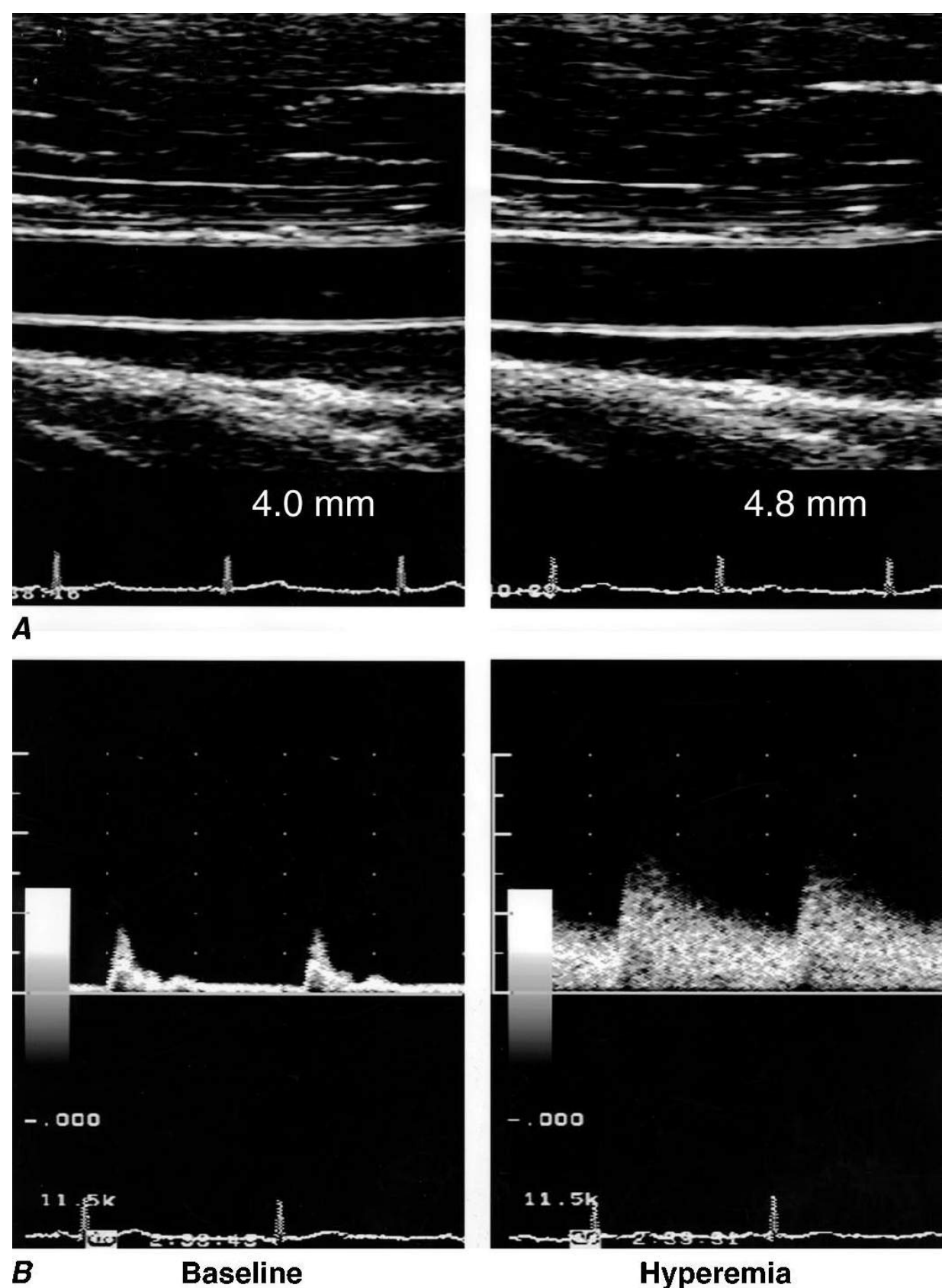


FIGURE 1-2

Assessment of endothelial function in vivo using blood pressure cuff occlusion and release. Upon deflation of the cuff, an ultrasound probe monitors changes in diameter (A) and blood flow (B) of the brachial artery (C). (Reproduced with permission of J. Vita, MD.)

TABLE 1-1

ENDOTHELIAL FUNCTIONS IN HEALTH AND DISEASE	
HOMEOSTATIC PROPERTIES	DYSFUNCTIONAL PROPERTIES
Optimize balance between vasodilation and vasoconstriction	Impaired dilation, vasoconstriction
Antithrombotic, profibrinolytic	Prothrombotic, antifibrinolytic
Anti-inflammatory	Proinflammatory
Antiproliferative	Proproliferative
Antioxidant	Prooxidant
Permselectivity	Impaired barrier function

production of reactive oxygen species, such as superoxide anion (O_2^-), by endothelial or smooth-muscle cells under pathologic conditions (e.g., excessive exposure to angiotensin II), can promote local oxidative stress and inactivate NO.

The endothelial monolayer contributes critically to inflammatory processes involved in normal host defenses and pathologic states. The normal endothelium resists prolonged contact with blood leukocytes; however, when activated by bacterial products such as endotoxin or by proinflammatory cytokines released during infection or injury, endothelial cells express an array of leukocyte adhesion molecules that bind various classes of leukocytes. The endothelial cells appear to recruit selectively different classes of leukocytes in different pathologic conditions. The gamut of adhesion molecules and chemokines generated during acute bacterial infection tends to recruit granulocytes. In chronic inflammatory diseases such as tuberculosis and atherosclerosis, endothelial cells express adhesion molecules that favor the recruitment of mononuclear leukocytes that characteristically accumulate in these conditions.

The endothelium also dynamically regulates thrombosis and hemostasis. NO, in addition to its vasodilatory properties, can limit platelet activation and aggregation. Like NO, prostacyclin produced by endothelial cells under normal conditions not only provides a vasodilatory stimulus but also antagonizes platelet activation and aggregation. Thrombomodulin expressed on the surface of endothelial cells binds thrombin at low concentrations and inhibits coagulation through activation of the protein C pathway, inactivating clotting factors Va and VIIIa and thus combating thrombus formation. The surface of endothelial cells contains heparan sulfate glycosaminoglycans that furnish an endogenous antithrombotic coating to the vasculature. Endothelial cells also participate actively in fibrinolysis and its regulation. They express receptors for plasminogen and plasminogen activators and produce

tissue-type plasminogen activator. Through local generation of plasmin, the normal endothelial monolayer can promote the lysis of nascent thrombi.

When activated by inflammatory cytokines, bacterial endotoxin, or angiotensin II, for example, endothelial cells can produce substantial quantities of the major inhibitor of fibrinolysis, plasminogen activator inhibitor 1 (PAI-1). Thus, in pathologic circumstances, the endothelial cell may promote local thrombus accumulation rather than combat it. Inflammatory stimuli also induce the expression of the potent procoagulant tissue factor, a contributor to disseminated intravascular coagulation in sepsis.

Endothelial cells also participate in the pathophysiology of a number of immune-mediated diseases. Lysis of endothelial cells mediated by complement provides an example of immunologically mediated tissue injury. The presentation of foreign histocompatibility complex antigens by endothelial cells in solid-organ allografts can promote allograft arteriopathy. In addition, immune-mediated endothelial injury may contribute in some patients with thrombotic thrombocytopenic purpura and patients with hemolytic-uremic syndrome. Thus, in addition to the involvement of innate immune responses, endothelial cells participate actively in both humoral and cellular limbs of the immune response.

Endothelial cells regulate growth of subjacent smooth-muscle cells. Heparan sulfate glycosaminoglycans elaborated by endothelial cells can inhibit smooth-muscle proliferation. In contrast, when exposed to various injurious stimuli, endothelial cells can elaborate growth factors and chemoattractants, such as platelet-derived growth factor, that can promote the migration and proliferation of vascular smooth-muscle cells. Dysregulated elaboration of these growth-stimulatory molecules may promote smooth-muscle accumulation in atherosclerotic lesions.

Vascular smooth-muscle cell

The vascular smooth-muscle cell, the major cell type of the media layer of blood vessels, also contributes actively to vascular pathobiology. Contraction and relaxation of smooth-muscle cells at the level of the muscular arteries controls blood pressure and, hence, regional blood flow and the afterload experienced by the left ventricle (see below). The vasomotor tone of veins, which is governed by smooth-muscle cell tone, regulates the capacitance of the venous tree and influences the preload experienced by both ventricles. Smooth-muscle cells in the adult vessel seldom replicate in the absence of arterial injury or inflammatory activation. Proliferation and migration of arterial smooth-muscle cells, associated with functional modulation characterized by lower content of contractile proteins and greater production of extracellular matrix macromolecules, can contribute to the development of arterial stenoses in atherosclerosis, arteriolar remodeling that can sustain and propagate hypertension, and the hyperplastic

response of arteries injured by percutaneous intervention. In the pulmonary circulation, smooth-muscle migration and proliferation contribute decisively to the pulmonary vascular disease that gradually occurs in response to sustained high-flow states such as left-to-right shunts. Such pulmonary vascular disease provides a major obstacle to the management of many patients with adult congenital heart disease. Among other mediators, microRNAs have emerged as powerful regulators of this transition, offering new targets for intervention.

Smooth-muscle cells secrete the bulk of vascular extracellular matrix. Excessive production of collagen and glycosaminoglycans contributes to the remodeling and altered functions and biomechanics of arteries affected by hypertension or atherosclerosis. In larger elastic arteries, the elastin synthesized by smooth-muscle cells serves to maintain not only normal arterial structure, but also hemodynamic function. The ability of the larger arteries, such as the aorta, to store the kinetic energy of systole promotes tissue perfusion during diastole. Arterial stiffness associated with aging or disease, as manifested by a widening pulse pressure, increases left ventricular afterload and portends a poor outcome.

Like endothelial cells, vascular smooth-muscle cells do not merely respond to vasomotor or inflammatory stimuli elaborated by other cell types but can themselves serve as a source of such stimuli. For example, when exposed to bacterial endotoxin or other proinflammatory stimuli, smooth-muscle cells can elaborate cytokines and other inflammatory mediators. Like endothelial cells, upon inflammatory activation, arterial smooth-muscle cells can produce prothrombotic mediators such as tissue factor, the antifibrinolytic protein PAI-1, and other molecules that modulate thrombosis and fibrinolysis. Smooth-muscle cells also elaborate autocrine growth factors that can amplify hyperplastic responses to arterial injury.

Vascular smooth-muscle cell function

Vascular smooth-muscle cells govern vessel tone. These cells contract when stimulated by a rise in intracellular calcium concentration by calcium influx through the plasma membrane and by calcium release from intracellular stores (**Fig. 1-3**). In vascular smooth-muscle cells, voltage-dependent L-type calcium channels open with membrane depolarization, which is regulated by energy-dependent ion pumps such as the Na^+, K^+ -ATPase pump and ion channels such as the Ca^{2+} -sensitive K^+ channel. Local changes in intracellular calcium concentration, termed calcium sparks, result from the influx of calcium through the voltage-dependent calcium channel and are caused by the coordinated activation of a cluster of ryanodine-sensitive calcium release channels in the sarcoplasmic reticulum (see below). Calcium sparks directly augment intracellular calcium concentration and

indirectly increase intracellular calcium concentration by activating chloride channels. In addition, calcium sparks reduce smooth-muscle contractility by activating large-conductance calcium-sensitive K^+ channels, hyperpolarizing the cell membrane and thereby limiting further voltage-dependent increases in intracellular calcium.

Biochemical agonists also increase intracellular calcium concentration, in this case by receptor-dependent activation of phospholipase C with hydrolysis of phosphatidylinositol 4,5-bisphosphate, resulting in the generation of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). These membrane lipid derivatives in turn activate protein kinase C and increase intracellular calcium concentration. In addition, IP_3 binds to specific receptors on the sarcoplasmic reticulum membrane to increase calcium efflux from this calcium storage pool into the cytoplasm.

Vascular smooth-muscle cell contraction depends principally on the phosphorylation of myosin light chain, which in the steady state, reflects the balance between the actions of myosin light chain kinase and myosin light chain phosphatase. Calcium activates myosin light chain kinase through the formation of a calcium-calmodulin complex. Phosphorylation of myosin light chain by this kinase augments myosin ATPase activity and enhances contraction. Myosin light chain phosphatase dephosphorylates myosin light chain, reducing myosin ATPase activity and contractile force. Phosphorylation of the myosin-binding subunit (thr695) of myosin light chain phosphatase by Rho kinase inhibits phosphatase activity and induces calcium sensitization of the contractile apparatus. Rho kinase is itself activated by the small GTPase RhoA, which is stimulated by guanine exchange factors and inhibited by GTPase-activating proteins.

Both cyclic AMP and cyclic GMP relax vascular smooth-muscle cells through complex mechanisms. β agonists, acting through their G-protein-coupled receptors activate adenylyl cyclase to convert ATP to cyclic AMP; NO and atrial natriuretic peptide acting directly and via a G-protein-coupled receptor, respectively, activate guanylyl cyclase to convert GTP to cyclic GMP. These agents in turn activate protein kinase A and protein kinase G, respectively, which inactivate myosin light chain kinase and decrease vascular smooth-muscle cell tone. In addition, protein kinase G can interact directly with the myosin-binding substrate subunit of myosin light chain phosphatase, increasing phosphatase activity and decreasing vascular tone. Finally, several mechanisms drive NO-dependent, protein kinase G-mediated reductions in vascular smooth-muscle cell calcium concentration, including phosphorylation-dependent inactivation of RhoA; decreased IP_3 formation; phosphorylation of the IP_3 receptor-associated cyclic GMP kinase substrate, with subsequent inhibition of IP_3 receptor function; phosphorylation of phospholamban, which increases calcium

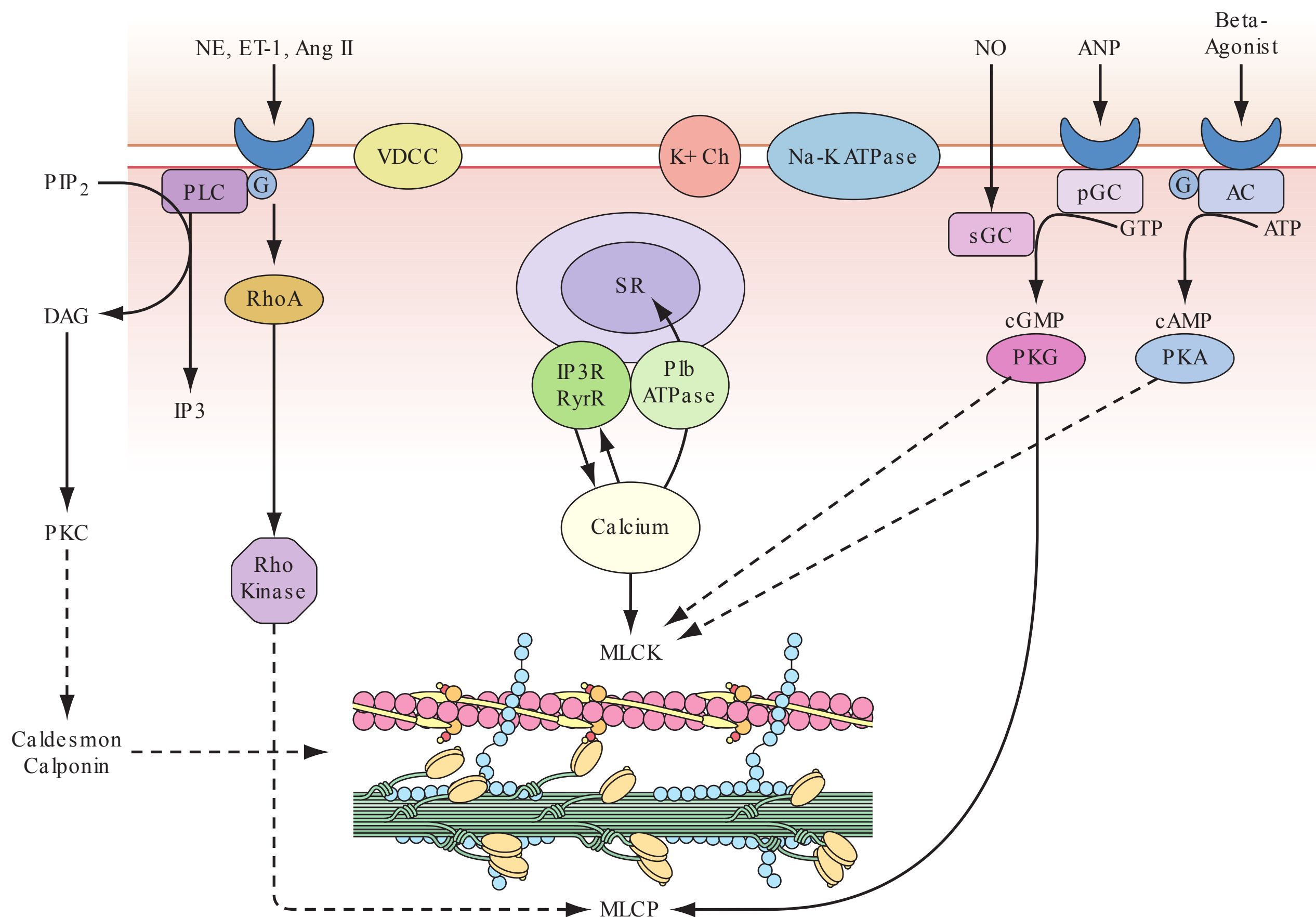


FIGURE 1-3

Regulation of vascular smooth-muscle cell calcium concentration and actomyosin ATPase-dependent contraction. AC, adenylyl cyclase; Ang II, angiotensin II; ANP, atrial natriuretic peptide; DAG, diacylglycerol; ET-1, endothelin-1; G, G protein; IP₃, inositol 1,4,5-trisphosphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NE, norepinephrine; NO, nitric oxide; pGC,

particular guanylyl cyclase; PIP₂, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; sGC, soluble guanylyl cyclase; SR, sarcoplasmic reticulum; VDCC, voltage-dependent calcium channel. (Modified from BBerk, in *Vascular Medicine*, 3rd ed. Philadelphia, Saunders, Elsevier, 2006, p. 23; with permission.)

ATPase activity and sequestration of calcium in the sarcoplasmic reticulum; and protein kinase G-dependent stimulation of plasma membrane calcium ATPase activity, perhaps by activation of the Na⁺,K⁺-ATPase pump or hyperpolarization of the cell membrane by activation of calcium-dependent K⁺ channels.

Control of vascular smooth-muscle cell tone

The autonomic nervous system and endothelial cells modulate vascular smooth-muscle cells in a tightly regulated manner. Autonomic neurons enter the blood vessel medial layer from the adventitia and modulate vascular smooth-muscle cell tone in response to baroreceptors and chemoreceptors within the aortic arch and carotid bodies and in response to thermoreceptors in the skin. These regulatory components include rapidly acting reflex arcs modulated by central inputs that respond to sensory inputs (olfactory, visual, auditory, and tactile) as well as

emotional stimuli. Three classes of nerves mediate autonomic regulation of vascular tone: sympathetic, whose principal neurotransmitters are epinephrine and norepinephrine; parasympathetic, whose principal neurotransmitter is acetylcholine; and nonadrenergic/noncholinergic, which include two subgroups—nitergic, whose principal neurotransmitter is NO, and peptidergic, whose principal neurotransmitters are substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and ATP.

Each of these neurotransmitters acts through specific receptors on the vascular smooth-muscle cell to modulate intracellular calcium and, consequently, contractile tone. Norepinephrine activates α receptors, and epinephrine activates α and β receptors (adrenergic receptors); in most blood vessels, norepinephrine activates postjunctional α_1 receptors in large arteries and α_2 receptors in small arteries and arterioles, leading to vasoconstriction. Most blood vessels express β_2 -adrenergic receptors on their vascular smooth-

muscle cells and respond to β agonists by cyclic AMP-dependent relaxation. Acetylcholine released from parasympathetic neurons binds to muscarinic receptors (of which there are five subtypes, M_{1-5}) on vascular smooth-muscle cells to yield vasorelaxation. In addition, NO stimulates presynaptic neurons to release acetylcholine, which can stimulate the release of NO from the endothelium. Nitrergic neurons release NO produced by neuronal NO synthase, which causes vascular smooth-muscle cell relaxation via the cyclic GMP-dependent and -independent mechanisms described above. The peptidergic neurotransmitters all potently vasodilate, acting either directly or through endothelium-dependent NO release to decrease vascular smooth-muscle cell tone.

The endothelium modulates vascular smooth-muscle tone by the direct release of several effectors, including NO, prostacyclin, hydrogen sulfide, and endothelium-derived hyperpolarizing factor, all of which cause vasorelaxation, and endothelin, which causes vasoconstriction. The release of these endothelial effectors of vascular smooth-muscle cell tone is stimulated by mechanical (shear stress, cyclic strain, etc.) and biochemical mediators (purinergic agonists, muscarinic agonists, peptidergic agonists), with the biochemical mediators acting through endothelial receptors specific to each class. In addition to these local paracrine modulators of vascular smooth-muscle cell tone, circulating mediators can affect tone, including norepinephrine and epinephrine, vasopressin, angiotensin II, bradykinin, and the natriuretic peptides (atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP], C-type natriuretic peptide [CNP], and dendroaspis natriuretic peptide [DNP]), as discussed above.

VASCULAR REGENERATION

Growth of new blood vessels can occur in response to conditions such as chronic hypoxemia and tissue ischemia. Growth factors, including vascular endothelial growth factor (VEGF) and forms of fibroblast growth factor (FGF), activate a signaling cascade that stimulates endothelial proliferation and tube formation, defined as angiogenesis. Guidance molecules, including members of the semaphorin family of secreted peptides, direct blood vessel patterning by attracting or repelling nascent endothelial tubes. The development of collateral vascular networks in the ischemic myocardium, an example of angiogenesis, can result from selective activation of endothelial progenitor cells, which may reside in the blood vessel wall or home to the ischemic tissue from the bone marrow. True arteriogenesis, or the development of a new blood vessel that includes all three cell layers, normally does not occur in the cardiovascular system of adult mammals. The molecular

mechanisms and progenitor cells that can recapitulate blood vessel development de novo are under rapidly advancing study.

VASCULAR PHARMACOGENOMICS

The last decade has witnessed considerable progress in efforts to define the genetic differences underlying individual variations in vascular pharmacologic responses. Many investigators have focused on receptors and enzymes associated with neurohumoral modulation of vascular function as well as hepatic enzymes that metabolize drugs that affect vascular tone. The genetic polymorphisms thus far associated with differences in vascular response often (but not invariably) relate to functional differences in the activity or expression of the receptor or enzyme of interest. Some of these polymorphisms appear to have different allele frequencies in specific ethnic groups.

CELLULAR BASIS OF CARDIAC CONTRACTION

CARDIAC ULTRASTRUCTURE

About three-fourths of the ventricular mass is composed of cardiomyocytes, normally 60–140 μm in length and 17–25 μm in diameter (**Fig. 1-4A**). Each cell contains multiple, rodlike cross-banded strands (myofibrils) that run the length of the cell and are composed of serially repeating structures, the sarcomeres. The cytoplasm between the myofibrils contains other cell constituents, including the single centrally located nucleus, numerous mitochondria, and the intracellular membrane system, the sarcoplasmic reticulum.

The sarcomere, the structural and functional unit of contraction, lies between adjacent Z lines, which are dark repeating bands that are apparent on transmission electron microscopy. The distance between Z lines varies with the degree of contraction or stretch of the muscle and ranges between 1.6 and 2.2 μm . Within the confines of the sarcomere are alternating light and dark bands, giving the myocardial fibers their striated appearance under the light microscope. At the center of the sarcomere is a dark band of constant length (1.5 μm), the A band, which is flanked by two lighter bands, the I bands, which are of variable length. The sarcomere of heart muscle, like that of skeletal muscle, consists of two sets of interdigitating myofilaments. Thicker filaments, composed principally of the protein myosin, traverse the A band; they are about 10 nm (100 Å) in diameter, with tapered ends. Thinner filaments, composed primarily of actin, course from the Z lines through the I band into the A band; they are approximately 5 nm (50 Å) in diameter and 1.0 μm in length.

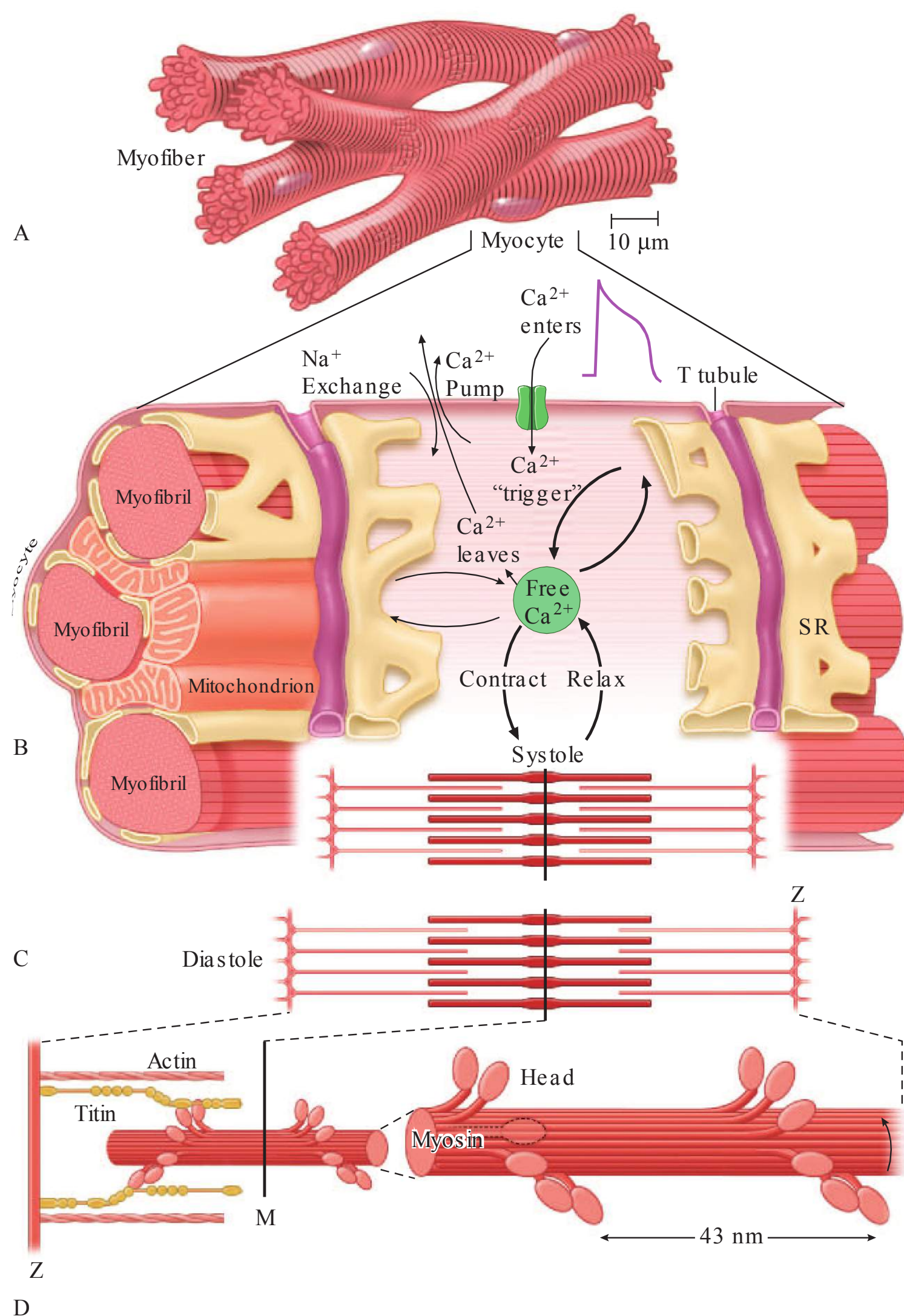


FIGURE 1-4

A shows the branching myocytes making up the cardiac myofibers. B illustrates the critical role played by the changing $[Ca^{2+}]$ in the myocardial cytosol. Ca^{2+} ions are schematically shown as entering through the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma. These Ca^{2+} ions “trigger” the release of more calcium from the sarcoplasmic reticulum (SR) and thereby initiate a contraction-relaxation cycle. Eventually the small quantity of Ca^{2+} that has entered the cell leaves predominantly through an Na^+/Ca^{2+} exchanger, with a lesser role for the sarcolemmal Ca^{2+} pump. The varying actin-myosin overlap is shown for (B) systole, when $[Ca^{2+}]$ is maximal, and (C) diastole, when $[Ca^{2+}]$ is minimal. D. The myosin heads, attached to the thick filaments, interact with the thin actin filaments. (From LH Opie: Heart Physiology: From Cell to Circulation, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004. Reprinted with permission. Copyright LH Opie, 2004.)

Thus, thick and thin filaments overlap only within the (dark) A band, whereas the (light) I band contains only thin filaments. On electron-microscopic examination, bridges may be seen to extend between the thick and thin filaments within the A band; these are myosin heads (see below) bound to actin filaments.

THE CONTRACTILE PROCESS

The sliding filament model for muscle contraction rests on the fundamental observation that both the thick and the thin filaments are constant in overall length during both contraction and relaxation. With activation, the actin filaments are propelled farther into the A band. In the process, the A band remains constant in length, whereas the I band shortens and the Z lines move toward one another.

The myosin molecule is a complex, asymmetric fibrous protein with a molecular mass of about 500,000 Da; it has a rodlike portion that is about 150 nm (1500 Å) in length with a globular portion (head) at its end. These globular portions of myosin form the bridges between the myosin

and actin molecules and are the site of ATPase activity. In forming the thick myofilament, which is composed of ~300 longitudinally stacked myosin molecules, the rodlike segments of the myosin molecules are laid down in an orderly, polarized manner, leaving the globular portions projecting outward so that they can interact with actin to generate force and shortening (Fig. 1-4B).

Actin has a molecular mass of about 47,000 Da. The thin filament consists of a double helix of two chains of actin molecules wound about each other on a larger molecule, tropomyosin. A group of regulatory proteins—troponins C, I, and T—are spaced at regular intervals on this filament (Fig. 1-5). In contrast to myosin, actin lacks intrinsic enzymatic activity but does combine reversibly with myosin in the presence of ATP and Ca^{2+} . The calcium ion activates the myosin ATPase, which in turn breaks down ATP, the energy source for contraction (Fig. 1-5). The activity of myosin ATPase determines the rate of forming and breaking of the actomyosin cross-bridges and ultimately the velocity of muscle contraction. In relaxed muscle, tropomyosin inhibits this interaction. Titin (Fig. 1-4D) is a large,

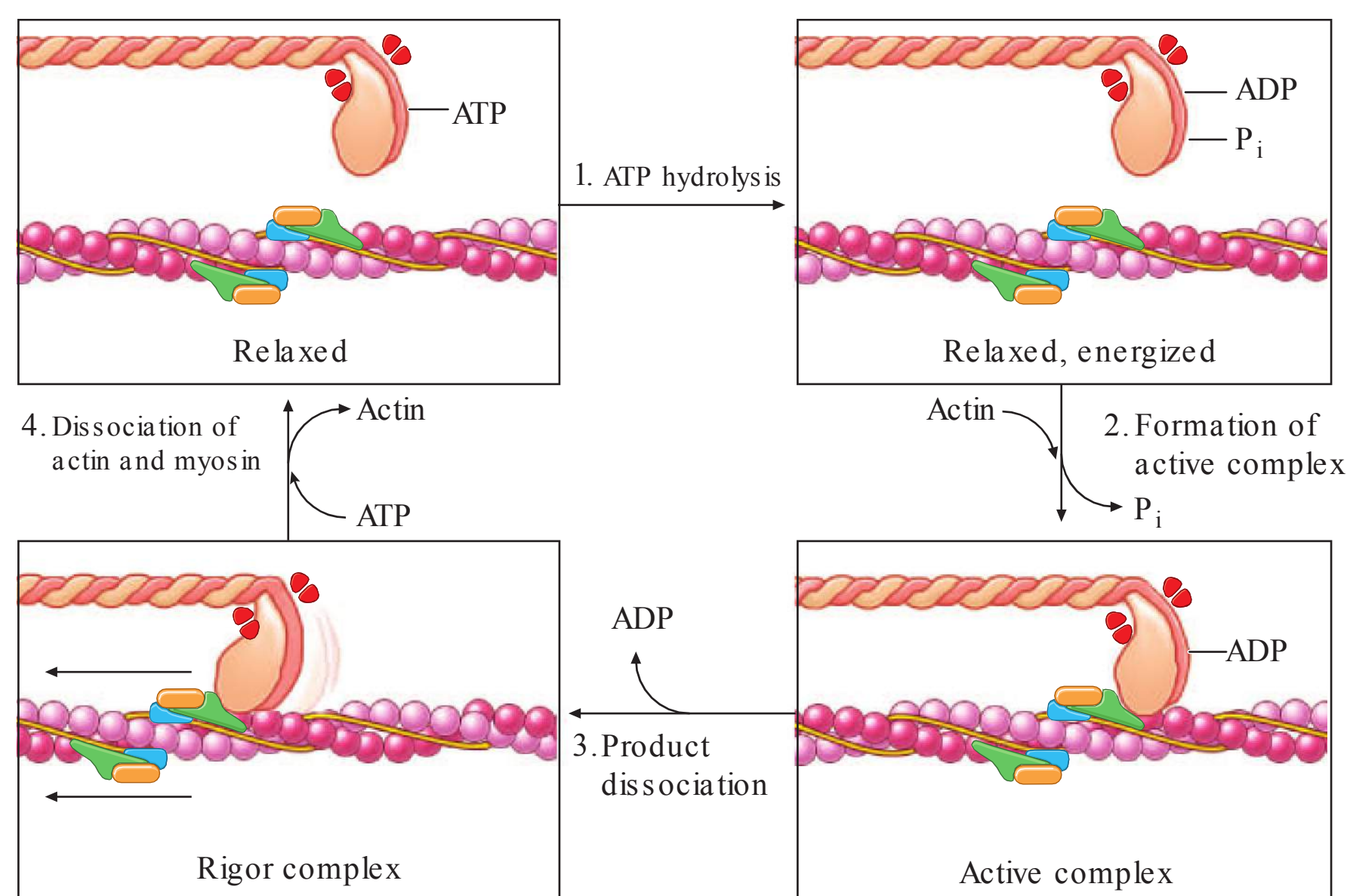


FIGURE 1-5

Four steps in cardiac muscle contraction and relaxation. In relaxed muscle (upper left), ATP bound to the myosin cross-bridge dissociates the thick and thin filaments. Step 1: Hydrolysis of myosin-bound ATP by the ATPase site on the myosin head transfers the chemical energy of the nucleotide to the activated cross-bridge (upper right). When cytosolic Ca^{2+} concentration is low, as in relaxed muscle, the reaction cannot proceed because tropomyosin and the troponin complex on the thin filament do not allow the active sites on actin to interact with the cross-bridges. Therefore, even though the cross-bridges are energized, they cannot interact with actin. Step 2: When Ca^{2+} binding to troponin C has exposed active sites on the thin filament, actin interacts with the myosin cross-bridges to form an active complex (lower right) in which the energy derived from ATP is retained in the actin-bound cross-bridge, whose orientation has not yet shifted. Step 3: The

muscle contracts when ADP dissociates from the cross-bridge. This step leads to the formation of the low-energy rigor complex (lower left) in which the chemical energy derived from ATP hydrolysis has been expended to perform mechanical work (the “rowing” motion of the cross-bridge). **Step 4:** The muscle returns to its resting state, and the cycle ends when a new molecule of ATP binds to the rigor complex and dissociates the cross-bridge from the thin filament. This cycle continues until calcium is dissociated from troponin C in the thin filament, which causes the contractile proteins to return to the resting state with the cross-bridge in the energized state. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase. (From AM Katz: *Heart failure: Cardiac function and dysfunction*, in *Atlas of Heart Diseases*, 3rd ed, WS Colucci [ed]. Philadelphia, Current Medicine, 2002. Reprinted with permission.)

flexible, myofibrillar protein that connects myosin to the Z line; its stretching contributes to the elasticity of the heart. Dystrophin is a long cytoskeletal protein that has an amino-terminal actin-binding domain and a carboxy-terminal domain that binds to the dystroglycan complex at adherens junctions on the cell membrane, thus tethering the sarcomere to the cell membrane at regions tightly coupled to adjacent contracting myocytes. Mutations in components of the dystrophin complex lead to muscular dystrophy and associated cardiomyopathy.

During activation of the cardiac myocyte, Ca^{2+} becomes attached to one of three components of the heterotrimer troponin C, which results in a conformational change in the regulatory protein tropomyosin; the latter, in turn, exposes the actin cross-bridge interaction sites (Fig. 1-5). Repetitive interaction between myosin heads and actin filaments is termed cross-bridge cycling, which results in sliding of the actin along the myosin filaments, ultimately causing muscle shortening and/or the development of tension. The splitting of ATP

then dissociates the myosin cross-bridge from actin. In the presence of ATP (Fig. 1-5), linkages between actin and myosin filaments are made and broken cyclically as long as sufficient Ca^{2+} is present; these linkages cease when $[\text{Ca}^{2+}]$ falls below a critical level, and the troponin-tropomyosin complex once more prevents interactions between the myosin cross-bridges and actin filaments (Fig. 1-6).

Intracytoplasmic Ca^{2+} is a principal determinant of the inotropic state of the heart. Most agents that stimulate myocardial contractility (positive inotropic stimuli), including the digitalis glycosides and β -adrenergic agonists, increase the $[\text{Ca}^{2+}]$ in the vicinity of the myofilaments, which in turn triggers cross-bridge cycling. Increased impulse traffic in the cardiac adrenergic nerves stimulates myocardial contractility as a consequence of the release of norepinephrine from cardiac adrenergic nerve endings. Norepinephrine activates myocardial β receptors and, through the G_s -stimulated guanine nucleotide-binding protein, activates the enzyme adenylyl cyclase, which leads to the formation

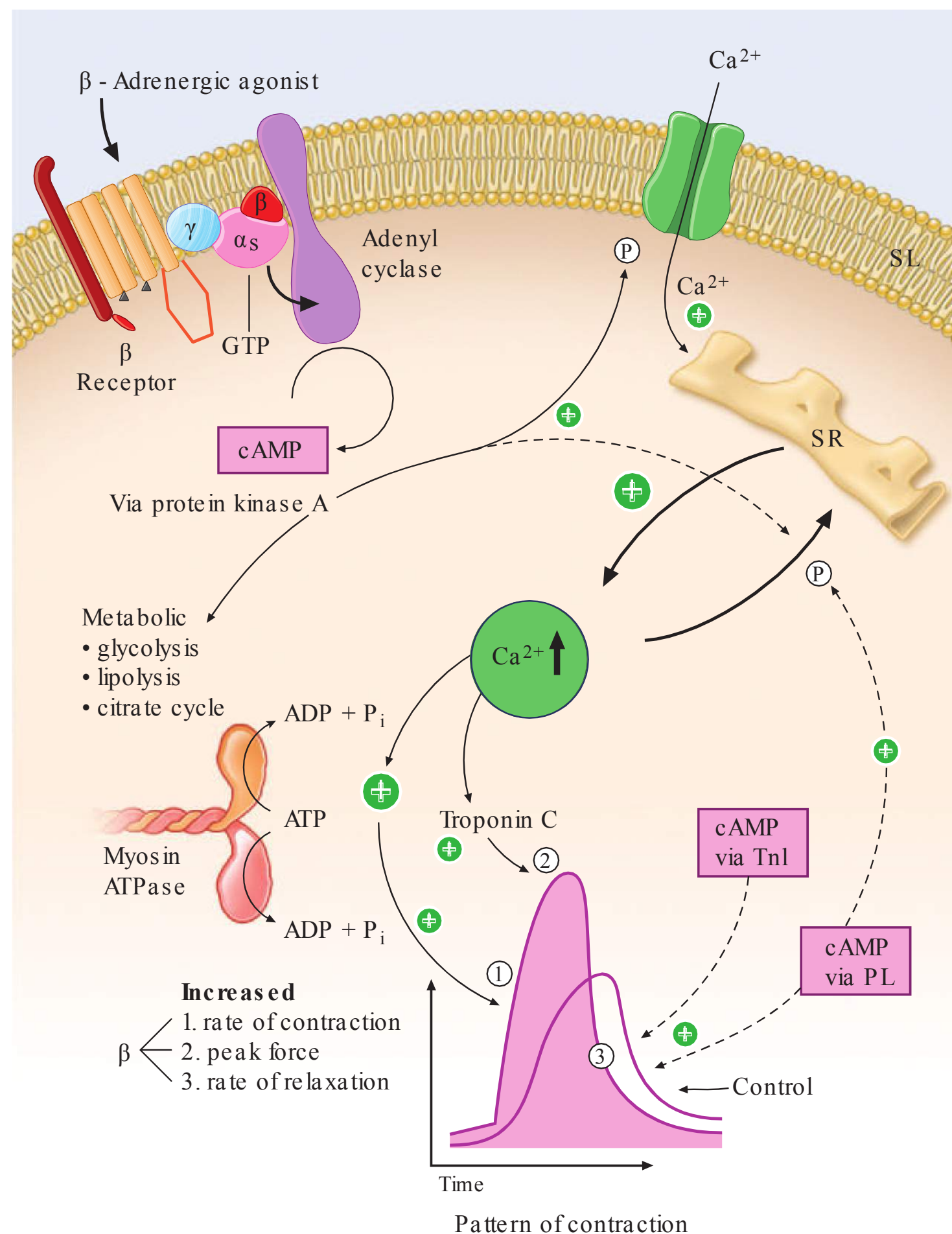


FIGURE 1-6

Signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects of β -adrenergic stimulation. When the β -adrenergic agonist interacts with the β receptor, a series of G protein-mediated changes leads to activation of adenylyl cyclase and the formation of cyclic adenosine monophosphate (cAMP). The latter acts via protein kinase A to stimulate metabolism (left) and phosphorylate the Ca^{2+} channel protein (right). The result is an enhanced opening probability of the Ca^{2+} channel, thereby increasing the inward movement of Ca^{2+} ions through the sarcolemma (SL) of the T tubule. These Ca^{2+} ions release more calcium from the sarcoplasmic reticulum (SR) to increase cytosolic Ca^{2+} and activate troponin C. Ca^{2+} ions also increase the rate of breakdown of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (P_i). Enhanced myosin ATPase activity explains the increased rate of contraction, with increased activation of troponin C explaining increased peak force development. An increased rate of relaxation results from the ability of cAMP to activate as well the protein phospholamban, situated on the membrane of the SR, that controls the rate of uptake of calcium into the SR. The latter effect explains enhanced relaxation (lusitropic effect). P, phosphorylation; PL, phospholamban; TnI, troponin I. (Modified from LH Opie: *Heart Physiology: From Cell to Circulation*, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004. Reprinted with permission. Copyright LH Opie, 2004.)

of the intracellular second messenger cyclic AMP from ATP (Fig. 1-6). Cyclic AMP in turn activates protein kinase A (PKA), which phosphorylates the Ca^{2+} channel in the myocardial sarcolemma, thereby enhancing the influx of Ca^{2+} into the myocyte. Other functions of PKA are discussed below.

The sarcoplasmic reticulum (SR) (Fig. 1-7), a complex network of anastomosing intracellular channels, invests the myofibrils. Its longitudinally disposed tubules closely invest the surfaces of individual sarcomeres but have no direct continuity with the outside of the cell. However, closely related to the SR, both structurally and functionally, are the transverse tubules, or T system, formed by tubelike invaginations of the sarcolemma that extend into the myocardial fiber along the Z lines, i.e., the ends of the sarcomeres.

CARDIAC ACTIVATION

In the inactive state, the cardiac cell is electrically polarized; i.e., the interior has a negative charge relative to the outside of the cell, with a transmembrane potential of -80 to -100 mV (Chap. 14). The sarcolemma, which in the resting state is largely impermeable to Na^+ , has a Na^+ - and K^+ -stimulating pump energized by ATP that extrudes Na^+ from the cell; this pump plays a critical role in establishing the resting potential. Thus, intracellular $[\text{K}^+]$ is relatively high and $[\text{Na}^+]$ is far lower; conversely, extracellular $[\text{Na}^+]$ is high and $[\text{K}^+]$ is low. At the same time, in the resting state, extracellular $[\text{Ca}^{2+}]$ greatly exceeds free intracellular $[\text{Ca}^{2+}]$.

The action potential has four phases (see Fig. 14-1B). During the plateau of the action potential (phase 2), there is a slow inward current through L-type Ca^{2+} channels in the sarcolemma (Fig. 1-7). The depolarizing current not only extends across the surface of the cell but penetrates deeply into the cell by way of the ramifying T tubular system. The absolute quantity of Ca^{2+} that crosses the sarcolemma and the T system is relatively small and by itself appears to be insufficient to bring about full activation of the contractile apparatus. However, this Ca^{2+} current triggers the release of much larger quantities of Ca^{2+} from the SR, a process termed Ca^{2+} -induced Ca^{2+} release. The latter is a major determinant of intracytoplasmic $[\text{Ca}^{2+}]$ and therefore of myocardial contractility.

Ca^{2+} is released from the SR through a Ca^{2+} release channel, a cardiac isoform of the ryanodine receptor (RyR2), which controls intracytoplasmic $[\text{Ca}^{2+}]$ and, as in vascular smooth-muscle cells, leads to the local changes in intracellular $[\text{Ca}^{2+}]$ called calcium sparks. A number of regulatory proteins, including calstabin 2, inhibit RyR2 and thereby the release of Ca^{2+} from the SR. PKA dissociates calstabin from the RyR2,

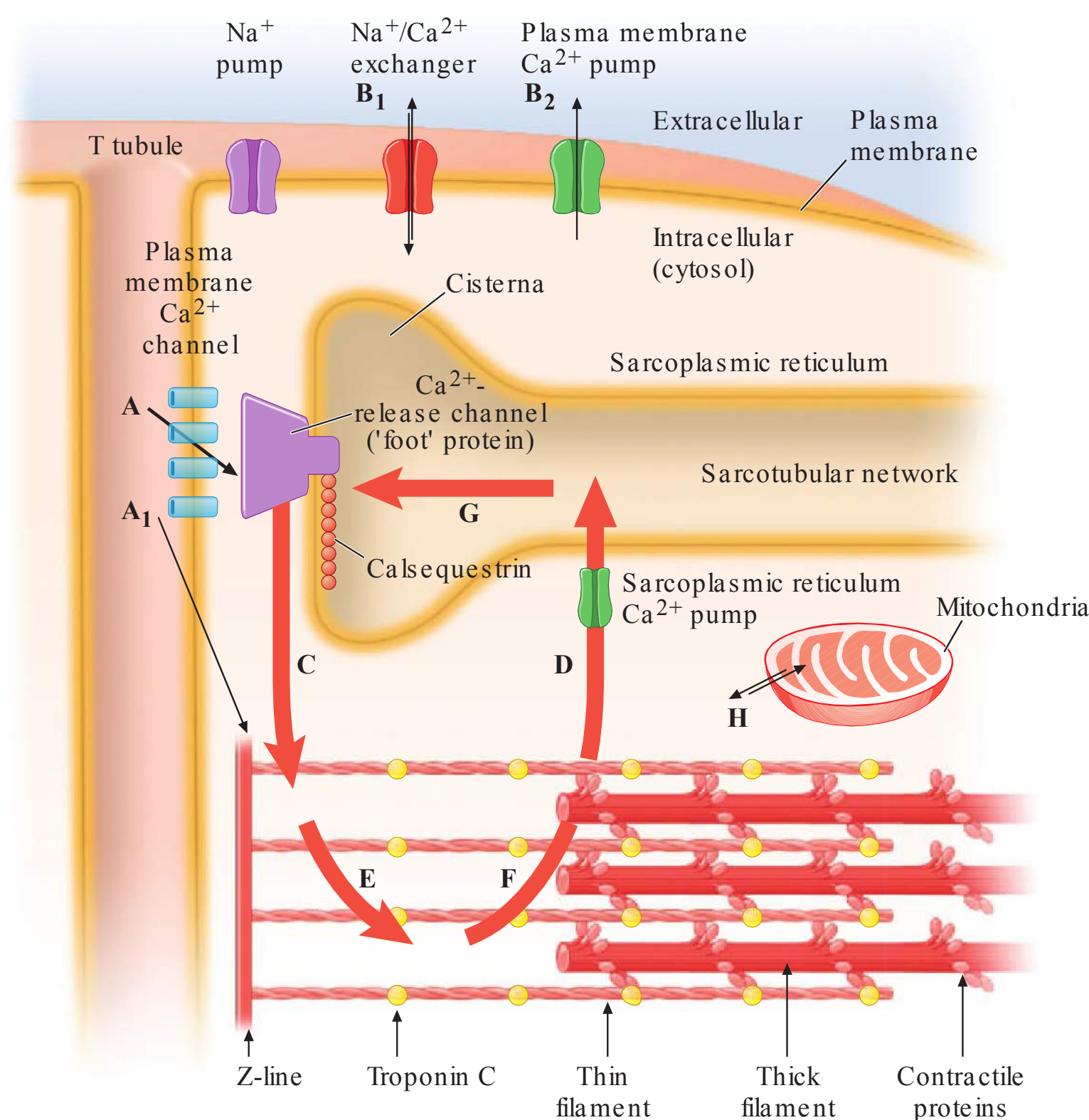


FIGURE 1-7

The Ca^{2+} fluxes and key structures involved in cardiac excitation-contraction coupling. The arrows denote the direction of Ca^{2+} fluxes. The thickness of each arrow indicates the magnitude of the calcium flux. Two Ca^{2+} cycles regulate excitation-contraction coupling and relaxation. The larger cycle is entirely intracellular and involves Ca^{2+} fluxes into and out of the sarcoplasmic reticulum, as well as Ca^{2+} binding to and release from troponin C. The smaller extracellular Ca^{2+} cycle occurs when this cation moves into and out of the cell. The action potential opens plasma membrane Ca^{2+} channels to allow passive entry of Ca^{2+} into the cell from the extracellular fluid (arrow A). Only a small portion of the Ca^{2+} that enters the cell directly activates the contractile proteins (arrow A₁). The extracellular cycle is completed when Ca^{2+} is actively transported back out to the extracellular fluid by way of two plasma membrane fluxes mediated by the sodium-calcium exchanger (arrow B₁) and the plasma membrane calcium pump (arrow B₂). In the intracellular Ca^{2+} cycle, passive Ca^{2+} release occurs through channels in the cisternae (arrow C) and initiates contraction; active Ca^{2+} uptake by the Ca^{2+} pump of the sarcotubular network (arrow D) relaxes the heart. Diffusion of Ca^{2+} within the sarcoplasmic reticulum (arrow G) returns this activator cation to the cisternae, where it is stored in a complex with calsequestrin and other calcium-binding proteins. Ca^{2+} released from the sarcoplasmic reticulum initiates systole when it binds to troponin C (arrow E). Lowering of cytosolic $[\text{Ca}^{2+}]$ by the sarcoplasmic reticulum (SR) causes this ion to dissociate from troponin (arrow F) and relaxes the heart. Ca^{2+} also may move between mitochondria and cytoplasm (H). (Adapted from AM Katz: *Physiology of the Heart*, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2005, with permission.)

enhancing Ca^{2+} release and thereby myocardial contractility. Excessive plasma catecholamine levels and cardiac sympathetic neuronal release of norepinephrine cause hyperphosphorylation of PKA, leading to calstabin 2-depleted RyR2. The latter depletes SR Ca^{2+} stores and thereby impairs cardiac contraction, leading to heart failure, and also triggers ventricular arrhythmias.

The Ca^{2+} released from the SR then diffuses toward the myofibrils, where, as already described, it combines with troponin C (Fig. 1-6). By repressing this inhibitor of contraction, Ca^{2+} activates the myofilaments to shorten. During repolarization, the activity of the Ca^{2+} pump in the SR, the SR Ca^{2+} ATPase (SERCA_{2A}), reaccumulates Ca^{2+} against a concentration gradient, and the Ca^{2+} is stored in the SR by its attachment to a protein, calsequestrin. This reaccumulation of Ca^{2+} is an energy (ATP)-requiring process that lowers the cytoplasmic $[\text{Ca}^{2+}]$ to a level that inhibits the actomyosin interaction responsible for contraction, and in this manner leads to myocardial relaxation. Also, there is an exchange of Ca^{2+} for Na^+ at the sarcolemma (Fig. 1-7), reducing the cytoplasmic $[\text{Ca}^{2+}]$. Cyclic AMP-dependent PKA phosphorylates the SR protein phospholamban; the latter, in turn, permits activation of the Ca^{2+} pump, thereby increasing the uptake of Ca^{2+} by the SR, accelerating the rate of relaxation, and providing larger quantities of Ca^{2+} in the SR for release by subsequent depolarization, thereby stimulating contraction.

Thus, the combination of the cell membrane, transverse tubules, and SR, with their ability to transmit the action potential and release and then reaccumulate Ca^{2+} , plays a fundamental role in the rhythmic contraction and relaxation of heart muscle. Genetic or pharmacologic alterations of any component, whatever its etiology, can disturb these functions.

CONTROL OF CARDIAC PERFORMANCE AND OUTPUT

The extent of shortening of heart muscle and, therefore, the stroke volume of the ventricle in the intact heart depend on three major influences: (1) the length of the muscle at the onset of contraction, i.e., the preload; (2) the tension that the muscle is called on to develop during contraction, i.e., the afterload; and (3) the contractility of the muscle, i.e., the extent and velocity of shortening at any given preload and afterload. The major determinants of preload, afterload, and contractility are shown in **Table 1-2**.

TABLE 1-2

DETERMINANTS OF STROKE VOLUME

I. Ventricular Preload

- A. Blood volume
- B. Distribution of blood volume
 - 1. Body position
 - 2. Intrathoracic pressure
 - 3. Intrapericardial pressure
 - 4. Venous tone
 - 5. Pumping action of skeletal muscles
- C. Atrial contraction

II. Ventricular Afterload

- A. Systemic vascular resistance
- B. Elasticity of arterial tree
- C. Arterial blood volume
- D. Ventricular wall tension
 - 1. Ventricular radius
 - 2. Ventricular wall thickness

III. Myocardial Contractility^a

- A. Intramyocardial $[Ca^{2+}] \uparrow \downarrow$
- B. Cardiac adrenergic nerve activity $\uparrow \downarrow^b$
- C. Circulating catecholamines $\uparrow \downarrow^b$
- D. Cardiac rate $\uparrow \downarrow^b$
- E. Exogenous inotropic agents $\uparrow$
- F. Myocardial ischemia $\downarrow$
- G. Myocardial cell death (necrosis, apoptosis, autophagy) $\downarrow$
- H. Alterations of sarcomeric and cytoskeletal proteins $\downarrow$
 - 1. Genetic
 - 2. Hemodynamic overload
- I. Myocardial fibrosis $\downarrow$
- J. Chronic overexpression of neurohormones $\downarrow$
- K. Ventricular remodeling $\downarrow$
- L. Chronic and/or excessive myocardial hypertrophy $\downarrow$

^aArrows indicate directional effects of determinants of contractility.

^bContractility rises initially but later becomes depressed.

THE ROLE OF MUSCLE LENGTH (PRELOAD)

The preload determines the length of the sarcomeres at the onset of contraction. The length of the sarcomeres associated with the most forceful contraction is $\sim 2.2 \mu\text{m}$. This length provides the optimum configuration for the interaction between the two sets of myofilaments. The length of the sarcomere also regulates the extent of activation of the contractile system, i.e., its sensitivity to Ca^{2+} . According to this concept, termed length-dependent activation, myofilament sensitivity to Ca^{2+} is also maximal at the optimal sarcomere length. The relation between the initial length of the muscle fibers and the developed force has prime importance for the function of heart muscle. This relationship forms the basis of Starling's law of the heart, which states

that within limits, the force of ventricular contraction depends on the end-diastolic length of the cardiac muscle; in the intact heart, the latter relates closely to the ventricular end-diastolic volume.

CARDIAC PERFORMANCE

The ventricular end-diastolic or “filling” pressure sometimes is used as a surrogate for the end-diastolic volume. In isolated heart and heart-lung preparations, the stroke volume varies directly with the end-diastolic fiber length (preload) and inversely with the arterial resistance (afterload), and as the heart fails—i.e., as its contractility declines—it delivers a progressively smaller stroke volume from a normal or even elevated end-diastolic volume. The relation between the ventricular end-diastolic pressure and the stroke work of the ventricle (the ventricular function curve) provides a useful definition of the level of contractility of the heart in the intact organism. An increase in contractility is accompanied by a shift of the ventricular function curve upward and to the left (greater stroke work at any level of ventricular end-diastolic pressure, or lower end-diastolic volume at any level of stroke work), whereas a shift downward and to the right characterizes depression of contractility (Fig. 1-8).

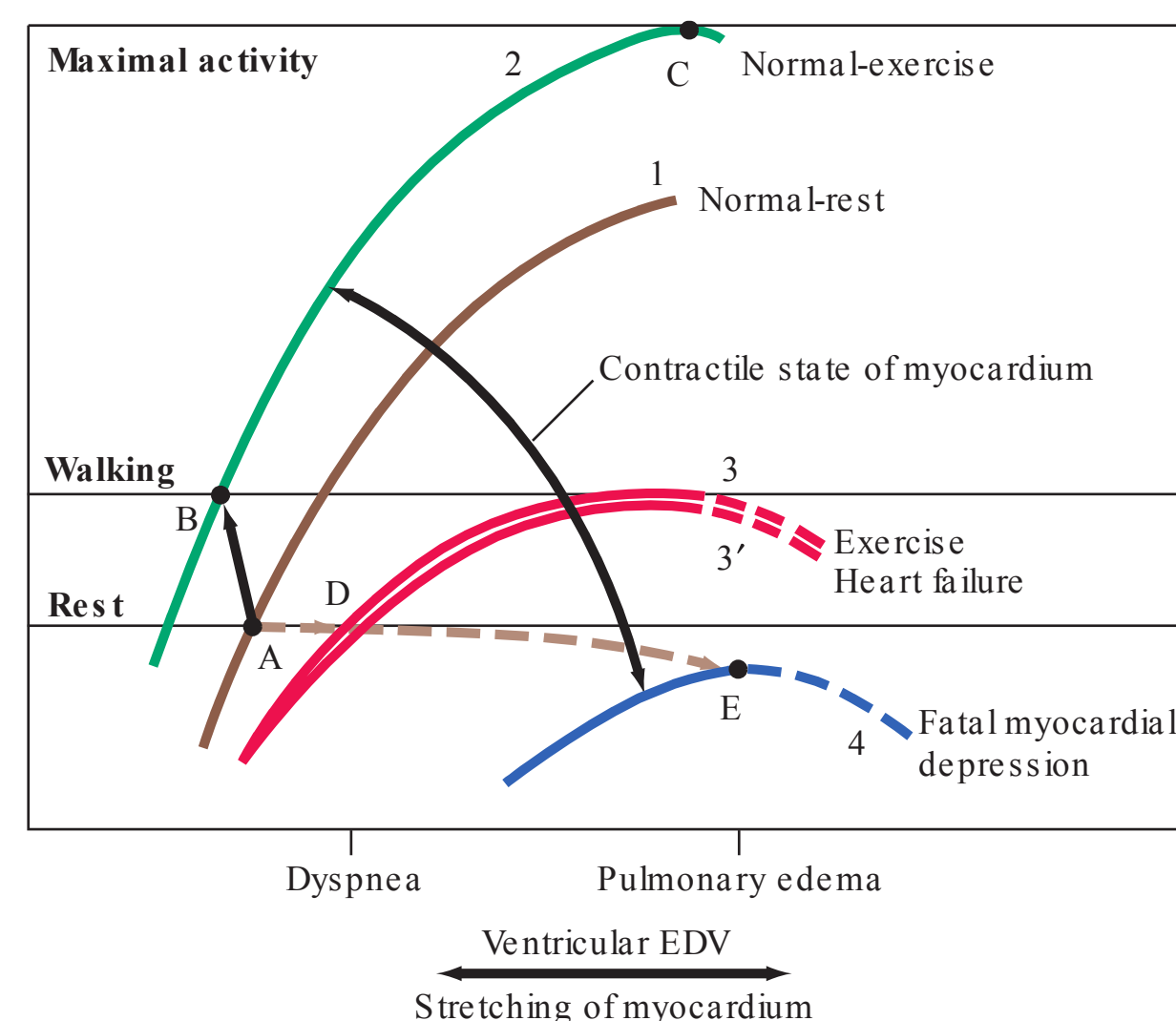


FIGURE 1-8

The interrelations among influences on ventricular end-diastolic volume (EDV) through stretching of the myocardium and the contractile state of the myocardium. Levels of ventricular EDV associated with filling pressures that result in dyspnea and pulmonary edema are shown on the abscissa. Levels of ventricular performance required when the subject is at rest, while walking, and during maximal activity are designated on the ordinate. The broken lines are the descending limbs of the ventricular-performance curves, which are rarely seen during life but show the level of ventricular performance if end-diastolic volume could be elevated to very high levels. For further explanation, see text. (Modified from WS Colucci and E Braunwald: *Pathophysiology of heart failure*, in Braunwald's Heart Disease, 7th ed, DP Zipes et al [eds]. Philadelphia: Elsevier, 2005, pp 509–538.)

VENTRICULAR AFTERLOAD

In the intact heart, as in isolated cardiac muscle, the extent and velocity of shortening of ventricular muscle fibers at any level of preload and of myocardial contractility relate inversely to the afterload, i.e., the load that opposes shortening. In the intact heart, the afterload may be defined as the tension developed in the ventricular wall during ejection. Afterload is determined by the aortic pressure as well as by the volume and thickness of the ventricular cavity. Laplace's law states that the tension of the myocardial fiber is the product of the intracavitary ventricular pressure and ventricular radius divided by wall thickness. Therefore, at any particular level of aortic pressure, the afterload on a dilated left ventricle exceeds that on a normal-sized ventricle. Conversely, at the same aortic pressure and ventricular diastolic volume, the afterload on a hypertrophied ventricle is lower than of a normal chamber. The aortic pressure in turn depends on the peripheral vascular resistance, the physical characteristics of the arterial tree, and the volume of blood it contains at the onset of ejection.

Ventricular afterload critically regulates cardiovascular performance (**Fig. 1-9**). As already noted, elevations

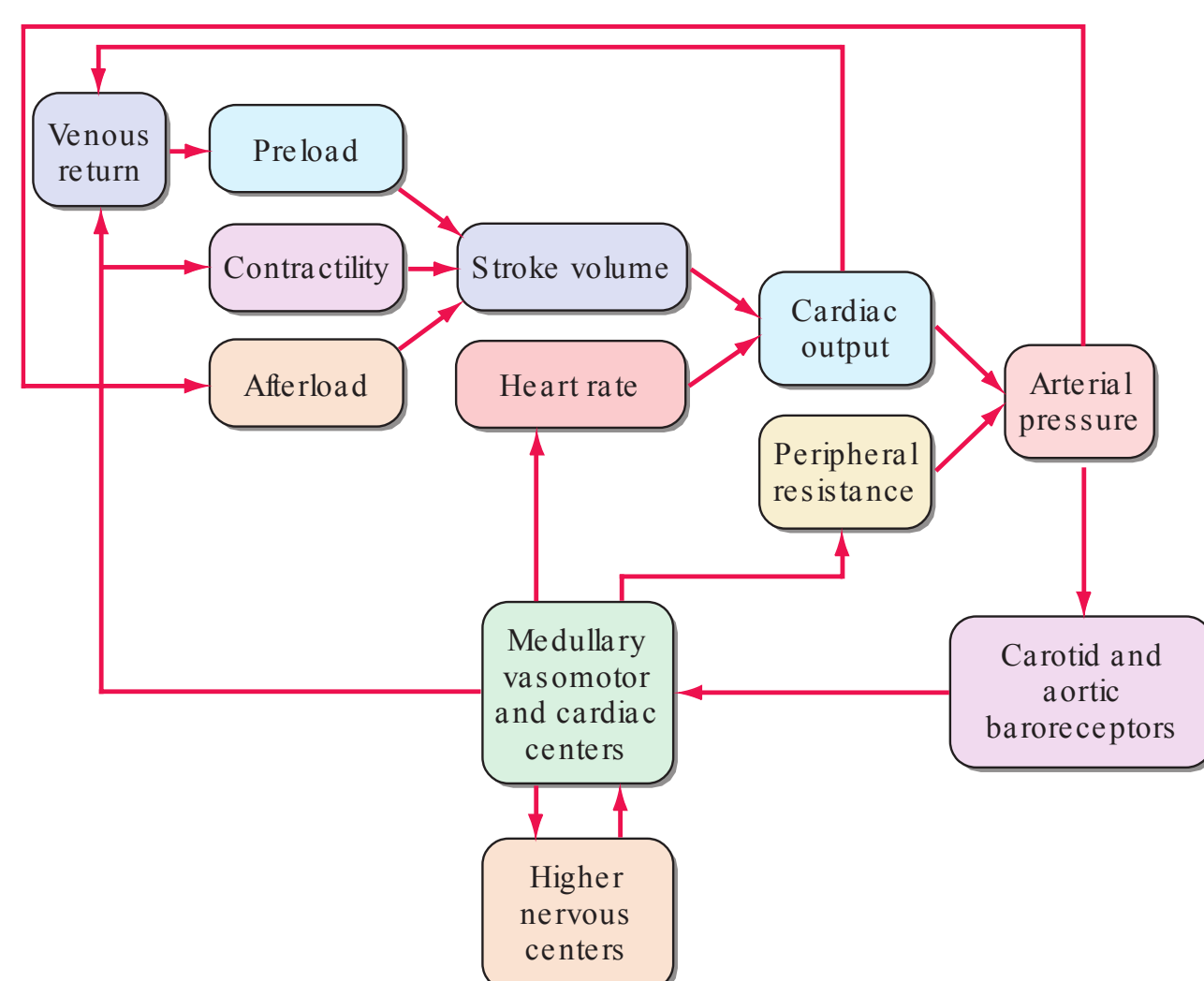


FIGURE 1-9

Interactions in the intact circulation of preload, contractility, and afterload in producing stroke volume. Stroke volume combined with heart rate determines cardiac output, which, when combined with peripheral vascular resistance, determines arterial pressure for tissue perfusion. The characteristics of the arterial system also contribute to afterload, an increase that reduces stroke volume. The interaction of these components with carotid and aortic arch baroreceptors provides a feedback mechanism to higher medullary and vasomotor cardiac centers and to higher levels in the central nervous system to effect a modulating influence on heart rate, peripheral vascular resistance, venous return, and contractility. (From MR Starling: *Physiology of myocardial contraction*, in *Atlas of Heart Failure: Cardiac Function and Dysfunction*, 3rd ed, WS Colucci and E Braunwald [eds]. Philadelphia: Current Medicine, 2002, pp 19–35.)

in both preload and contractility increase myocardial fiber shortening, whereas increases in afterload reduce it. The extent of myocardial fiber shortening and left ventricular size determine stroke volume. An increase in arterial pressure induced by vasoconstriction, for example, augments afterload, which opposes myocardial fiber shortening, reducing stroke volume.

When myocardial contractility becomes impaired and the ventricle dilates, afterload rises (Laplace's law) and limits cardiac output. Increased afterload also may result from neural and humoral stimuli that occur in response to a fall in cardiac output. This increased afterload may reduce cardiac output further, thereby increasing ventricular volume and initiating a vicious circle, especially in patients with ischemic heart disease and limited myocardial O_2 supply. Treatment with vasodilators has the opposite effect; when afterload is reduced, cardiac output rises (**Chap. 19**).

Under normal circumstances, the various influences acting on cardiac performance enumerated above interact in a complex fashion to maintain cardiac output at a level appropriate to the requirements of the metabolizing tissues (Fig. 1-9); interference with a single mechanism may not influence the cardiac output. For example, a moderate reduction of blood volume or the loss of the atrial contribution to ventricular contraction ordinarily can be sustained without a reduction in the cardiac output at rest. Under these circumstances, other factors, such as increases in the frequency of adrenergic nerve impulses to the heart, heart rate, and venous tone, will serve as compensatory mechanisms and sustain cardiac output in a normal individual.

EXERCISE

The integrated response to exercise illustrates the interactions among the three determinants of stroke volume: preload, afterload, and contractility (Fig. 1-8). Hyperventilation, the pumping action of the exercising muscles, and venoconstriction during exercise all augment venous return and hence ventricular filling and preload (Table 1-2). Simultaneously, the increase in the adrenergic nerve impulse traffic to the myocardium, the increased concentration of circulating catecholamines, and the tachycardia that occur during exercise combine to augment the contractility of the myocardium (Fig. 1-8, curves 1 and 2) and together elevate stroke volume and stroke work, without a change in or even a reduction of end-diastolic pressure and volume (Fig. 1-8, points A and B). Vasodilation occurs in the exercising muscles, thus tending to limit the increase in arterial pressure that otherwise would occur as cardiac output rises to levels as high as five times greater than basal levels during maximal exercise. This vasodilation ultimately allows the achievement of a greatly elevated

cardiac output during exercise at an arterial pressure only moderately higher than in the resting state.

ASSESSMENT OF CARDIAC FUNCTION

Several techniques can define impaired cardiac function in clinical practice. The cardiac output and stroke volume may be depressed in the presence of heart failure, but not uncommonly, these variables are within normal limits in this condition. A somewhat more sensitive index of cardiac function is the ejection fraction, i.e., the ratio of stroke volume to end-diastolic volume (normal value = $67 \pm 8\%$), which is frequently depressed in systolic heart failure even when the stroke volume itself is normal. Alternatively, abnormally elevated ventricular end-diastolic volume (normal value = $75 \pm 20 \text{ mL/m}^2$) or end-systolic volume (normal value = $25 \pm 7 \text{ mL/m}^2$) signifies impairment of left ventricular systolic function.

Noninvasive techniques, particularly echocardiography as well as radionuclide scintigraphy and cardiac magnetic resonance imaging (MRI) (**Chap. 12**), have great value in the clinical assessment of myocardial function. They provide measurements of end-diastolic and end-systolic volumes, ejection fraction, and systolic shortening rate, and they allow assessment of ventricular filling (see below) as well as regional contraction and relaxation. The latter measurements are particularly important in ischemic heart disease, as myocardial infarction causes regional myocardial damage.

A limitation of measurements of cardiac output, ejection fraction, and ventricular volumes in assessing

cardiac function is that ventricular loading conditions strongly influence these variables. Thus, a depressed ejection fraction and lowered cardiac output may occur in patients with normal ventricular function but reduced preload, as occurs in hypovolemia, or with increased afterload, as occurs in acutely elevated arterial pressure.

The end-systolic left ventricular pressure-volume relationship is a particularly useful index of ventricular performance because it does not depend on preload and afterload (**Fig. 1-10**). At any level of myocardial contractility, left ventricular end-systolic volume varies inversely with end-systolic pressure; as contractility declines, end-systolic volume (at any level of end-systolic pressure) rises.

DIASTOLIC FUNCTION

Ventricular filling is influenced by the extent and speed of myocardial relaxation, which in turn depends on the rate of uptake of Ca^{2+} by the SR; the latter may be enhanced by adrenergic activation and reduced by ischemia, which reduces the ATP available for pumping Ca^{2+} into the SR (see above). The stiffness of the ventricular wall also may impede filling. Ventricular stiffness increases with hypertrophy and conditions that infiltrate the ventricle, such as amyloid, or is caused by an extrinsic constraint (e.g., pericardial compression) (**Fig. 1-11**).

Ventricular filling can be assessed by continuously measuring the velocity of flow across the mitral valve using Doppler ultrasound. Normally, the velocity of inflow is more rapid in early diastole than during atrial systole; with mild to moderately impaired relaxation, the rate of early diastolic filling declines, whereas the rate of presystolic

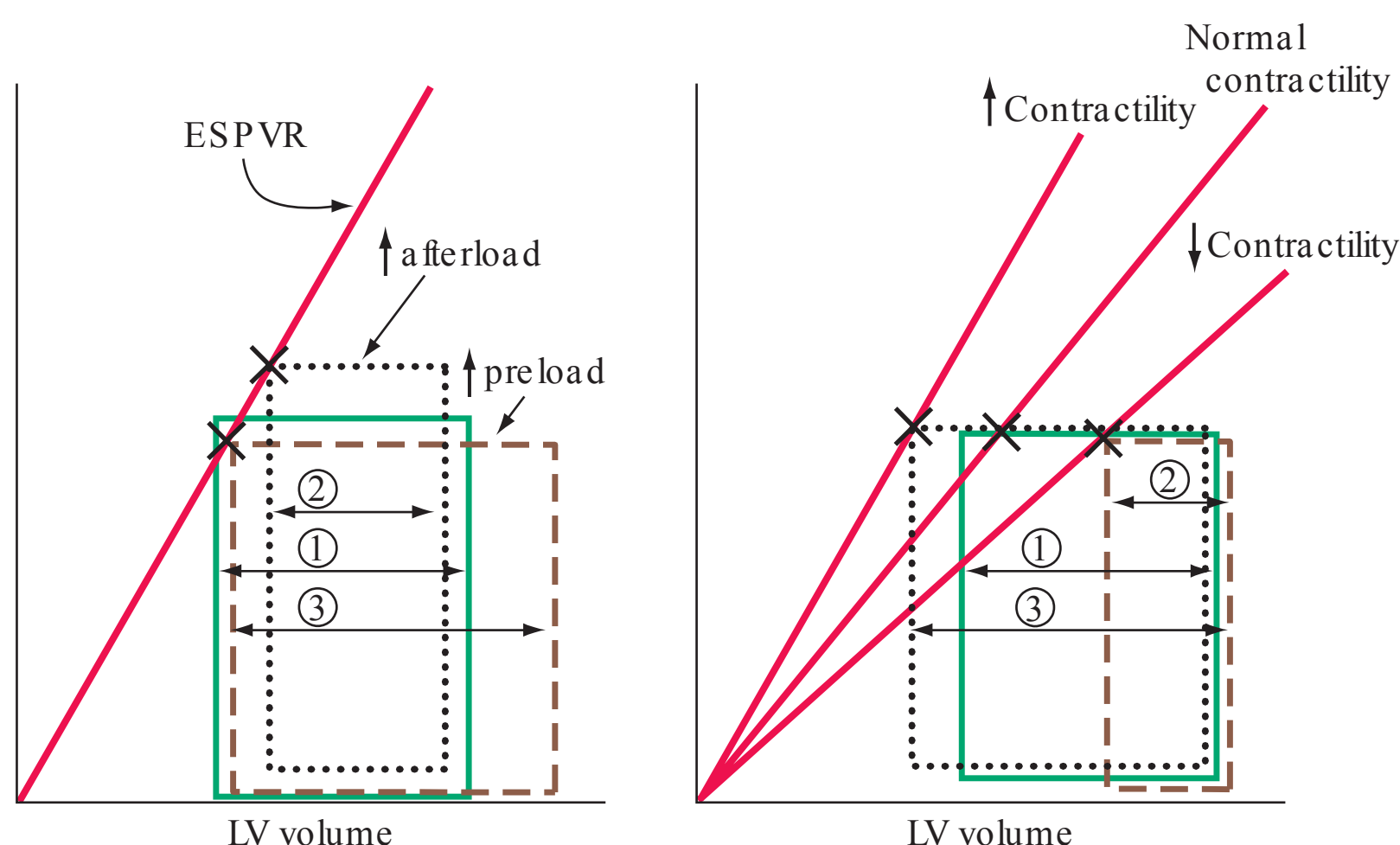


FIGURE 1-10

The responses of the left ventricle to increased afterload, increased preload, and increased and reduced contractility are shown in the pressure-volume plane. Left. Effects of increases in preload and afterload on the pressure-volume loop. Because there has been no change in contractility, the end-systolic pressure-volume relationship (ESPVR) is unchanged. With an increase in afterload, stroke volume falls (1 → 2); with an increase

in preload, stroke volume rises (1 → 3). Right. With increased myocardial contractility and constant left ventricular end-diastolic volume, the ESPVR moves to the left of the normal line (lower end-systolic volume at any end-systolic pressure) and stroke volume rises (1 → 3). With reduced myocardial contractility, the ESPVR moves to the right; end-systolic volume is increased, and stroke volume falls (1 → 2).

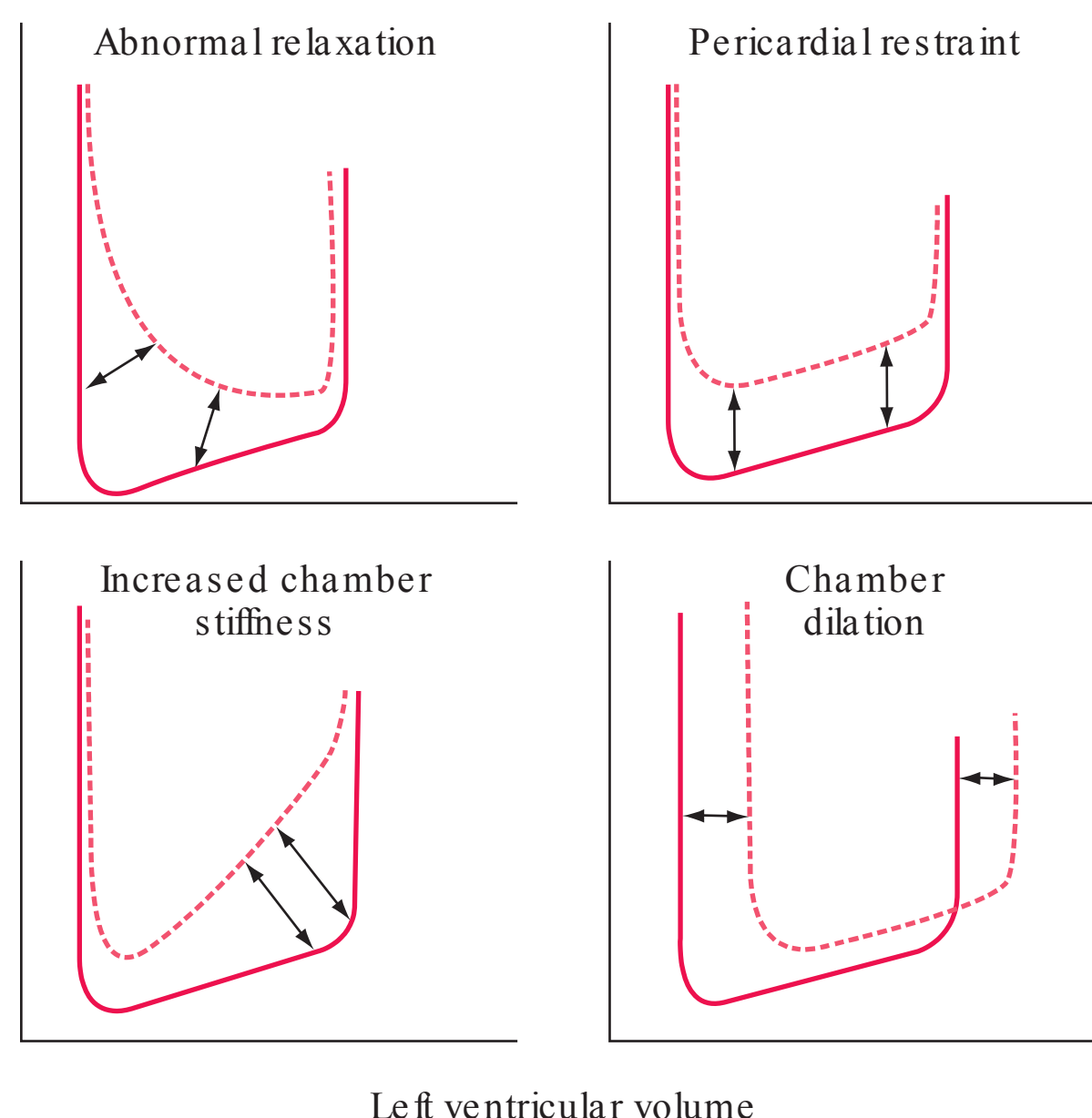


FIGURE 1-11

Mechanisms that cause diastolic dysfunction reflected in the pressure-volume relation. The bottom half of the pressure-volume loop is depicted. Solid lines represent normal subjects; broken lines represent patients with diastolic dysfunction. (From JD Carroll et al: The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. *Circulation* 74:815, 1986; with permission.)

filling rises. With further impairment of filling, the pattern is “pseudo-normalized,” and early ventricular filling becomes more rapid as left atrial pressure upstream to the stiff left ventricle rises.

CARDIAC METABOLISM

The heart requires a continuous supply of energy (in the form of ATP) not only to perform its mechanical pumping functions, but also to regulate intracellular and transsarcolemmal ionic movements and concentration gradients. Among its pumping functions, the development of tension, the frequency of contraction, and the level of myocardial contractility are the principal determinants of the heart's substantial energy needs, making its O_2 requirements approximately 15% of that of the entire organism.

Most ATP production depends on the oxidation of substrate (glucose and free fatty acids [FFAs]). Myocardial FFAs are derived from circulating FFAs, which result principally from lipolysis in adipose tissue, whereas the myocyte's glucose derives from plasma as well as from the cell's breakdown of its glycogen stores (glycogenolysis). These two principal sources of acetyl coenzyme A in cardiac muscle vary reciprocally. Glucose is broken down in the cytoplasm into a three-carbon product, pyruvate, which passes into

the mitochondria, where it is metabolized to the two-carbon fragment, acetyl-CoA, and undergoes oxidation. FFAs are converted to acyl-CoA in the cytoplasm and acetyl-CoA in the mitochondria. Acetyl-CoA enters the citric acid (Krebs) cycle to produce ATP by oxidative phosphorylation within the mitochondria; ATP then enters the cytoplasm from the mitochondrial compartment. Intracellular ADP, resulting from the breakdown of ATP, enhances mitochondrial ATP production.

In the fasted, resting state, circulating FFA concentrations and their myocardial uptake are high, and they furnish most of the heart's acetyl-CoA (~70%). In the fed state, with elevations of blood glucose and insulin, glucose oxidation increases and FFA oxidation subsides. Increased cardiac work, the administration of inotropic agents, hypoxia, and mild ischemia all enhance myocardial glucose uptake, glucose production resulting from glycogenolysis, and glucose metabolism to pyruvate (glycolysis). By contrast, β -adrenergic stimulation, as occurs during stress, raises the circulating levels and metabolism of FFAs in favor of glucose. Severe ischemia inhibits the cytoplasmic enzyme pyruvate dehydrogenase, and despite both glycogen and glucose breakdown, glucose is metabolized only to lactic acid (anaerobic glycolysis), which does not enter the citric acid cycle. Anaerobic glycolysis produces much less ATP than does aerobic glucose metabolism, in which glucose is metabolized to pyruvate and subsequently oxidized to CO_2 . High concentrations of circulating FFAs, which can occur when adrenergic stimulation is superimposed on severe ischemia, reduce oxidative phosphorylation and also cause ATP wastage; the myocardial content of ATP declines and impairs myocardial contraction. In addition, products of FFA breakdown can exert toxic effects on cardiac cell membranes and may be arrhythmogenic.

Myocardial energy is stored as creatine phosphate (CP), which is in equilibrium with ATP, the immediate source of energy. In states of reduced energy availability, the CP stores decline first. Cardiac hypertrophy, fibrosis, tachycardia, increased wall tension resulting from ventricular dilation, and increased intracytoplasmic $[Ca^{2+}]$ all contribute to increased myocardial energy needs. When coupled with reduced coronary flow reserve, as occurs with obstruction of coronary arteries or abnormalities of the coronary microcirculation, an imbalance in myocardial ATP production relative to demand may occur, and the resulting ischemia can worsen or cause heart failure.

Developmental biology of the cardiovascular system

The heart is the first organ to form during embryogenesis (Fig. 1-12) and must accomplish the simultaneous challenges of circulating blood, nutrients, and oxygen to the other forming organs while continuing to grow and undergo complex morphogenetic changes. Early

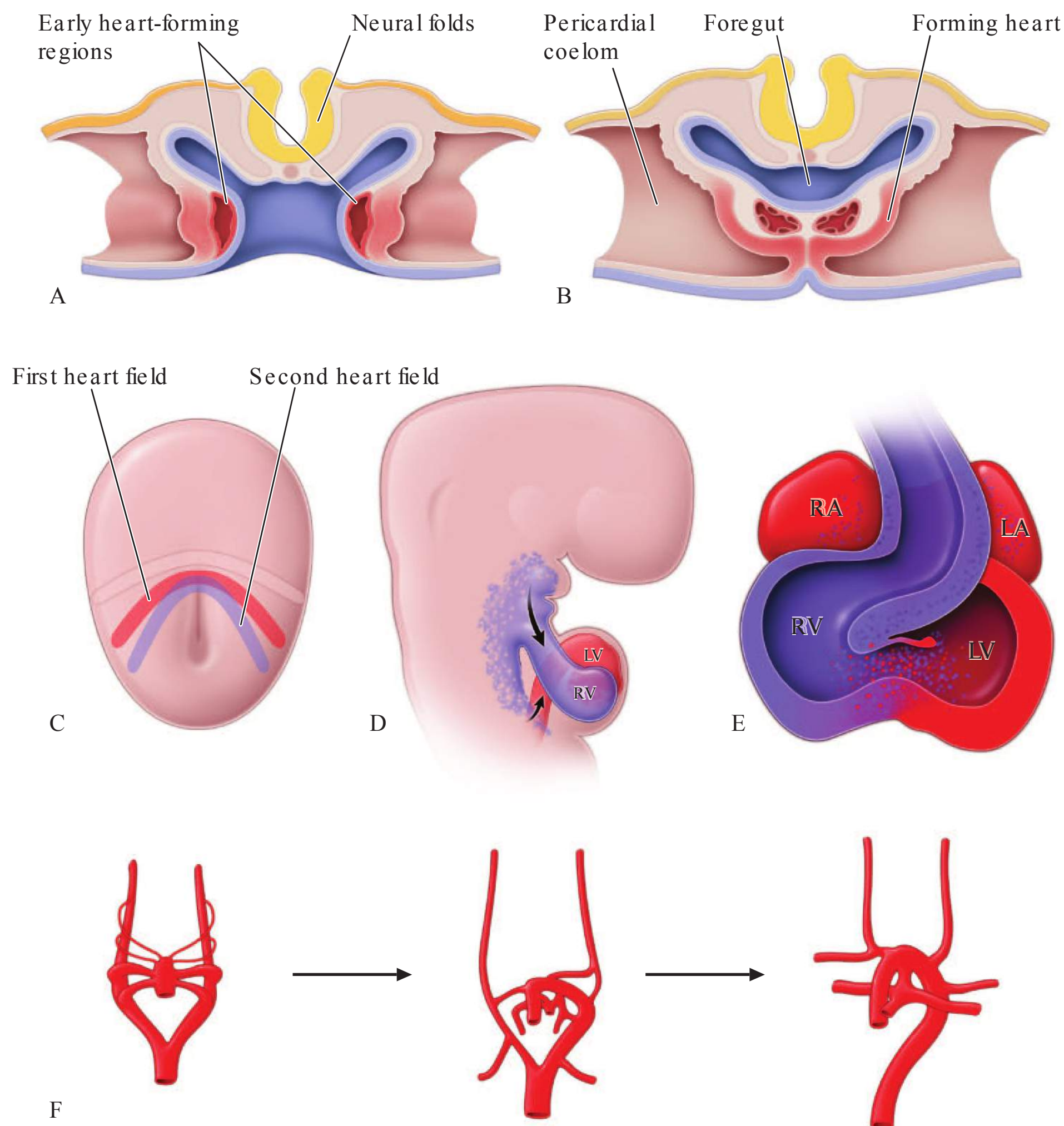


FIGURE 1-12

A. Schematic depiction of a transverse section through an early embryo depicts the bilateral regions where early heart tubes form. B. The bilateral heart tubes subsequently migrate to the midline and fuse to form the linear heart tube. C. At the early cardiac crescent stage of embryonic development, cardiac precursors include a primary heart field fated to form the linear heart tube and a second heart field fated to add myocardium to the inflow and outflow poles of the heart. D. Second heart field cells

populate the pharyngeal region before subsequently migrating to the maturing heart. E. Large portions of the right ventricle and outflow tract and some cells within the atria derive from the second heart field. F. The aortic arch arteries form as symmetric sets of vessels that then remodel under the influence of the neural crest to form the asymmetric mature vasculature. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

progenitors of the heart arise within very early crescent-shaped fields of lateral splanchnic mesoderm under the influence of multiple signals, including those derived from neural ectoderm long before neural tube closure. Early cardiac precursors express genes encoding regulatory transcription factors that play reiterated roles in cardiac development, such as NKX2-5 and GATA4. Mutations in these genes are responsible for some forms of inherited congenital heart disease. Cardiac precursors coalesce to form a midline heart tube composed of a single cell layer of endocardium surrounded by a single layer of myocardial precursors. The caudal, inflow region of the heart tube, which is destined

to adopt a more rostral final position, represents the atrial anlagen, whereas the rostral, outflow portion of the tube forms the truncus arteriosus, which divides to produce the aorta and the proximal pulmonary artery. Between these extremes lie the structural precursors of the ventricles.

The linear heart tube undergoes an asymmetric looping process (the first gross evidence of left-right asymmetry in the developing embryo), which positions the portion of the heart tube destined to become the left ventricle to the left of the more rostral precursors of the right ventricle and outflow tract. Looping is coordinated with chamber specification and ballooning of

various regions of the heart tube to produce the presumptive atria and ventricles.

Relatively recent work has demonstrated that significant portions of the right ventricle are formed by cells that are added to the developing heart after looping has occurred. These cells, which are derived from what is called the second heart field, migrate to the heart from the ventral pharynx and express markers that allow for their identification, including *Islet-1*. Different embryologic origins of cells within the right and left ventricles may help explain why some forms of congenital and adult heart diseases affect these regions of the heart to varying degrees.

After looping and chamber formation, a series of septation events divide the left and right sides of the heart, separate the atria from the ventricles, and form the aorta and pulmonary artery from the truncus arteriosus. Cardiac valves form between the atria and the ventricles and between the ventricles and the outflow vessels. Early in development, the single layer of myocardial cells secretes an extracellular matrix rich in hyaluronic acid. This extracellular matrix, termed “cardiac jelly,” accumulates within the endocardial cushions, precursors of the cardiac valves. Signals from overlying myocardial cells, including members of the transforming growth factor β family, trigger migration, invasion, and phenotypic changes of underlying endocardial cells, which undergo an epithelial-mesenchymal transformation and invade the cardiac jelly to cellularize the endocardial cushions. Mesenchymal components proliferate and remodel to form the mature valve leaflets.

The great vessels form as a series of bilaterally symmetric aortic arch arteries that undergo asymmetric remodeling events to form the mature vasculature. The immigration of neural crest cells that arise in the dorsal neural tube orchestrates this process. These cells are required for aortic arch remodeling and septation of the truncus arteriosus. They develop into smooth-muscle cells within the tunica media of the aortic arch, the ductus arteriosus, and the carotid arteries. Smooth-muscle cells within the descending aorta arise from a different embryologic source, the lateral plate mesoderm, and smooth muscle of the proximal outflow tract arises from the second heart field. Neural crest cells are sensitive to both vitamin A and folic acid, and congenital heart disease involving abnormal remodeling of the aortic arch arteries has been associated with maternal deficiencies of these vitamins. Congenital heart disease involving the outflow tract can be associated with other defects of neural crest, such as cleft palate or craniofacial abnormalities.

Coronary artery formation requires yet another cell population that initiates extrinsic to the embryonic heart fields. Epicardial cells arise in the proepicardial organ, a derivative of the septum transversum, which also contributes to the fibrous portion of the diaphragm

and to the liver. Proepicardial cells contribute to the smooth-muscle cells of the coronary arteries and are required for their proper patterning. Other cell types within the heart, including fibroblasts and potentially some myocardial and endocardial cells, also can arise from the proepicardium.

The cardiac conduction system, which functions both to generate and to propagate electrical impulses, develops primarily from multipotential cardiac precursors, which also give rise to cardiac muscle. The conduction system is composed of slow-conducting (proximal) components, such as the sinoatrial (SA) and atrioventricular (AV) nodes, as well as fast-conducting (distal) components, including the His bundle, bundle branches, and Purkinje fibers. The AV node primarily serves to delay the electrical impulse between atria and ventricles (manifesting decremental conduction), whereas the distal conduction system rapidly delivers the impulse throughout the ventricles. Significant recent attention has been focused on the embryologic origins of various components of the specialized conduction network. Precursors within the sinus venosus give rise to the SA node, whereas those within the AV canal mature into heterogeneous cell types that compose the AV node. Myocardial cells transdifferentiate into Purkinje fibers to form the distal conduction system. Fast and slow conducting cell types within the nodes and bundles are characterized by expression of distinct gap junction proteins, including connexins, and ion channels that characterize unique cell fates and electrical properties of the tissues. Developmental defects in conduction system morphogenesis and lineage determination can lead to various electrophysiologic disorders, including congenital heart block and preexcitation syndromes such as the Wolff-Parkinson-White syndrome (**Chap. 17**).

Studies of cardiac stem and progenitor cells suggest that progressive lineage restriction results in the gradual and stepwise determination of mature cell fates within the heart, with early precursors capable of adopting endothelial, smooth-muscle, or cardiac phenotypes, and subsequent further specialization into atrial, ventricular, and specialized conduction cell types.

REGENERATING CARDIAC TISSUE

Until very recently, adult mammalian myocardial cells were viewed as fully differentiated and without regenerative potential. Evidence currently supports the existence of limited regenerative potential of the mature heart. Considerable current effort is being devoted to evaluating the utility of various putative stem cell populations and regenerative approaches to enhance cardiac repair after injury. The success of such approaches would offer the exciting possibility of reconstructing an infarcted or failing ventricle.

CHAPTER 2

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE



Thomas A. Gaziano ■ J. Michael Gaziano

Cardiovascular disease (CVD) is now the most common cause of death worldwide. Before 1900, infectious diseases and malnutrition were the most common causes, and CVD was responsible for less than 10% of all deaths. In 2010, CVD accounted for approximately 16 million deaths worldwide (30%), including nearly 40% of deaths in high-income countries and about 28% in low- and middle-income countries.

THE EPIDEMIOLOGIC TRANSITION



The global rise in CVD is the result of an unprecedented transformation in the causes of morbidity and mortality during the twentieth century. Known as the epidemiologic transition, this shift is driven by industrialization, urbanization, and associated lifestyle changes and is taking place in every part of the world among all races, ethnic groups, and cultures. The transition is divided into four basic stages: pestilence and famine, receding pandemics, degenerative and man-made diseases, and delayed degenerative diseases. A fifth stage, characterized by an epidemic of inactivity and obesity, is emerging in some countries ([Table 2-1](#)).

The age of pestilence and famine is marked by malnutrition, infectious diseases, and high infant and child mortality that are offset by high fertility. Tuberculosis, dysentery, cholera, and influenza are often fatal, resulting in a mean life expectancy of about 30 years. CVD, which accounts for less than 10% of deaths, takes the form of rheumatic heart disease and cardiomyopathies due to infection and malnutrition. Approximately 10% of the world's population remains in the age of pestilence and famine.

Per capita income and life expectancy increase during the age of receding pandemics as the emergence of public health systems, cleaner water supplies, and improved nutrition combine to drive down deaths from infectious disease and malnutrition. Infant and

childhood mortality also decline, but deaths due to CVD increase to between 10 and 35% of all deaths. Rheumatic valvular disease, hypertension, coronary heart disease (CHD), and stroke are the predominant forms of CVD. Almost 40% of the world's population is currently in this stage.

The age of degenerative and man-made diseases is distinguished by mortality from noncommunicable diseases—primarily CVD—surpassing mortality from malnutrition and infectious diseases. Caloric intake, particularly from animal fat, increases. CHD and stroke are prevalent, and between 35 and 65% of all deaths can be traced to CVD. Typically, the rate of CHD deaths exceeds that of stroke by a ratio of 2:1 to 3:1. During this period, average life expectancy surpasses the age of 50. Roughly 35% of the world's population falls into this category.

In the age of delayed degenerative diseases, CVD and cancer remain the major causes of morbidity and mortality, with CVD accounting for 40% of all deaths. However, age-adjusted CVD mortality declines, aided by preventive strategies (for example, smoking cessation programs and effective blood pressure control), acute hospital management, and technologic advances, such as the availability of bypass surgery. CHD, stroke, and congestive heart failure are the primary forms of CVD. About 15% of the world's population is now in the age of delayed degenerative diseases or is exiting this age and moving into the fifth stage of the epidemiologic transition.

In the industrialized world, physical activity continues to decline while total caloric intake increases. The resulting epidemic of overweight and obesity may signal the start of the age of inactivity and obesity. Rates of type 2 diabetes mellitus, hypertension, and lipid abnormalities are on the rise, trends that are particularly evident in children. If these risk factor trends continue, age-adjusted CVD mortality rates could increase in the coming years.

TABLE 2-1

FIVE STAGES OF THE EPIDEMIOLOGIC TRANSITION			
STAGE	DESCRIPTION	DEATHS RELATED TO CVD, %	PREDOMINANT CVD TYPE
Pestilence and famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths related to malnutrition and infection; precipitous decline in infant and child mortality rates	10–35	Rheumatic valvular disease, hypertension, CHD, and stroke (predominantly hemorrhagic)
Degenerative and man-made diseases	Increased fat and caloric intake and decrease in physical activity lead to emergence of hypertension and atherosclerosis; with increase in life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious disease	35–65	CHD and stroke (ischemic and hemorrhagic)
Delayed degenerative diseases	CVD and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events; age-adjusted CVD mortality declines; CVD affecting older and older individuals	40–50	CHD, stroke, and congestive heart failure
Inactivity and obesity	Overweight and obesity increase at alarming rate; diabetes and hypertension increase; decline in smoking rates levels of ; a minority of the population meets physical activity recommendations	33	CHD, stroke, and congestive heart failure, peripheral vascular disease

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.
Source: Adapted from AR Omran: The epidemiologic transition: A theory of the epidemiology of population change. Milbank Mem Fund Q 49:509, 1971; and SJ Olshansky, AB Ault: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. Milbank Q 64:355, 1986.

PATTERNS IN THE EPIDEMIOLOGIC TRANSITION

Unique regional features have modified aspects of the transition in various parts of the world. High-income countries experienced declines in CVD death rates by as much as 50–60% over the last 60 years, whereas CVD death rates increased by 15% over the past 20 years in the low- and middle-income range. However, given the large amount of available data, the United States serves as a useful reference point for comparisons. The age of pestilence and famine occurred before 1900, with a

largely agrarian economy and population. Infectious diseases accounted for more deaths than any other cause. By the 1930s, the country proceeded through the age of receding pandemics. The establishment of public health infrastructures resulted in dramatic declines in infectious disease mortality rates. Lifestyle changes due to rapid urbanization resulted in a simultaneous increase in CVD mortality rates, reaching approximately 390 per 100,000. Between 1930 and 1965, the country entered the age of degenerative and man-made diseases. Infectious disease mortality rates fell to fewer than 50 per 100,000 per year, whereas CVD mortality rates reached

peak levels with increasing urbanization and lifestyle changes in diet, physical activity, and tobacco consumption. The age of delayed degenerative diseases took place between 1965 and 2000. New therapeutic approaches, preventive measures, and exposure to public health campaigns promoting lifestyle modifications led to substantial declines in age-adjusted mortality rates and a steadily rising age at which a first CVD event occurs.



Currently, the United States is entering what appears to be a fifth phase. The decline in the age-adjusted CVD death rate of 3% per year through the 1970s and 1980s has tapered off in the 1990s to 2%. However, CVD death rates have declined by 3–5% per year during the first decade of the new millennium. Competing trends appear to be at play. On the one hand, an increase in the prevalence of diabetes and obesity, a slowing in the rate of decline in smoking, and a leveling off in the rate of detection and treatment for hypertension are in the negative column. On the other hand, cholesterol levels continue to decline in the face of increased statin use.

Many high-income countries (HICs)—which together account for 15% of the population—have proceeded through four stages of the epidemiologic transition in roughly the same pattern as the United States. CHD is the dominant form of CVD in these countries, with rates that tend to be two- to five-fold higher than stroke rates. However, variations exist. Whereas North America, Australia, and central northwestern European HICs experienced significant increases then rapid

declines in CVD rates, southern and central European countries experienced a more gradual rise and fall in rates. More specifically, central European countries (i.e., Austria, Belgium, and Germany) declined at slower rates compared to their northern counterparts (i.e., Finland, Sweden, Denmark, and Norway). Countries such as Portugal, Spain, and Japan never reached the high mortality rates that the United States and other countries did, with CHD mortality rates at 200 per 100,000, or less. The countries of Western Europe also exhibit a clear north/south gradient in absolute rates of CVD, with rates highest in northern countries (i.e., Finland, Ireland, and Scotland) and lowest in Mediterranean countries (i.e., France, Spain, and Italy). Japan is unique among the HICs, most likely due to the unique dietary patterns of its population. Although stroke rates increased dramatically, CHD rates did not rise as sharply in Japan. However, Japanese dietary habits are undergoing substantial changes, reflected in an increase in cholesterol levels.

Patterns in low- and middle-income countries (LMICs; gross national income per capita less than U.S. \$12,615) depend, in part, on cultural differences, secular trends, and responses at the country level, with regard to both public health and treatment infrastructure. Although communicable diseases continue to be a major cause of death, CVD has emerged as a significant health concern in LMICs. With 85% of the world's population, LMICs are driving the rates of change in the global burden of CVD (Fig. 2-1). In most LMICs, an

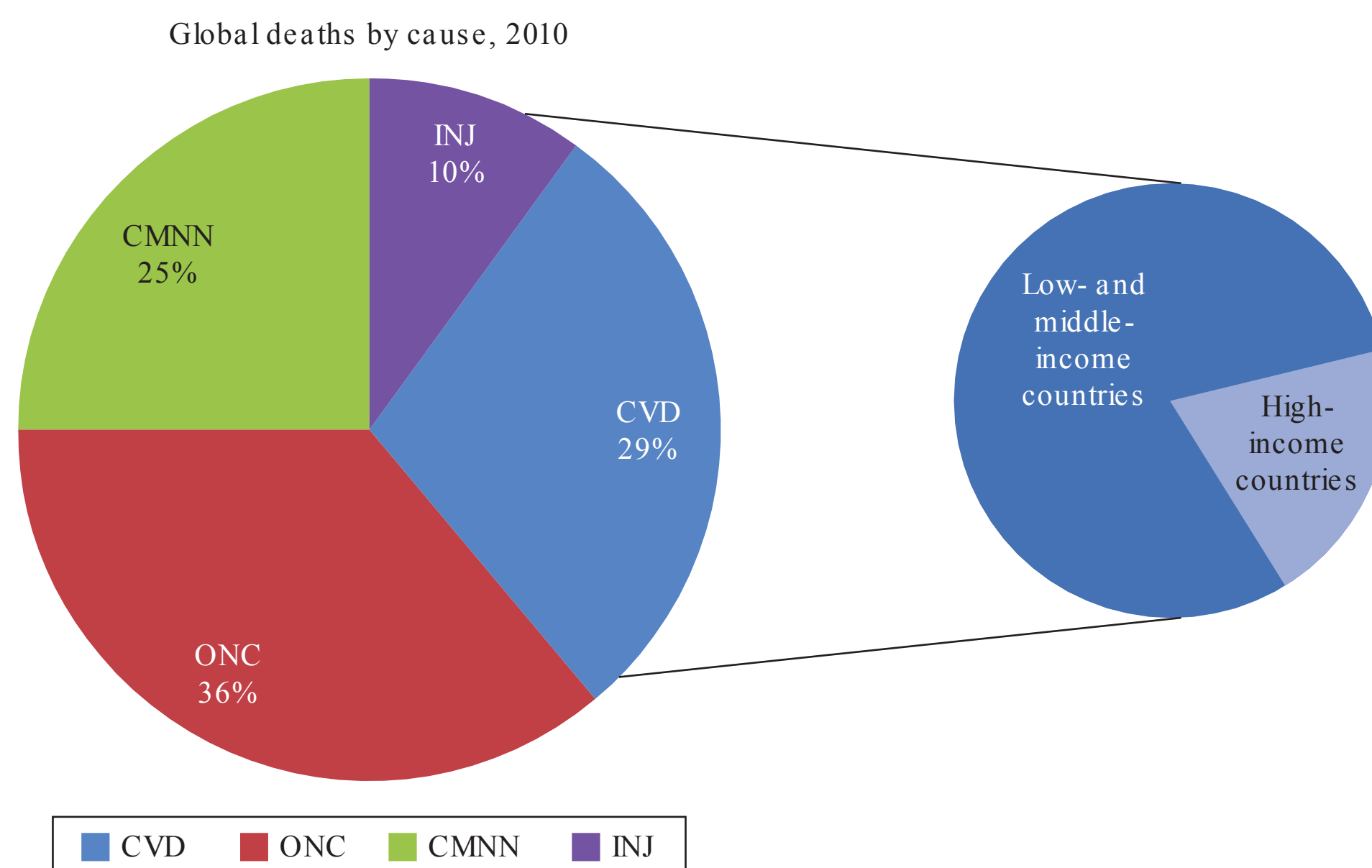


FIGURE 2-1

Global deaths by cause, 2010. CMNN, communicable, maternal, neonatal, and nutritional disorders; CVD, cardiovascular diseases; INJ, injuries; ONC, other noncommunicable diseases. (Based on

data from Global Burden of Disease Study 2010: Global Burden of Disease Study 2010 Mortality Results 1970–2010. Seattle, Institute for Health Metrics and Evaluation, 2012.)

urban/rural gradient has emerged for CHD, stroke, and hypertension, with higher rates in urban centers.

However, although CVD rates are rapidly rising, vast differences exist among the regions and countries, and even within the countries themselves (Fig. 2-2). The East Asia and Pacific regions appear to be straddling the second and third phases of the epidemiologic transition. CVD is a major cause of death in China, but like Japan, stroke causes more deaths than CHD in a ratio of about three to one. Vietnam and Cambodia, on the other hand, are just emerging from the pestilence and famine transition. The Middle East and North Africa regions also appear to be entering the third phase of the epidemiologic transition, with increasing life expectancy and CVD death rates just below those of HICs. In general, Latin America appears to be in the third phase of the transition, although there is vast regional heterogeneity with some areas in the second phase of the transition and some in the fourth. The Eastern Europe and Central Asia regions, however, are firmly in the peak of the third phase, with the highest death rates due to CVD (~66%) in the world. Importantly, deaths

due to CHD are not limited to the elderly in this region and have a significant effect on working-age populations. South Asia—and more specifically, India, which accounts for the greatest proportion of the region's population—is experiencing an alarming increase in heart disease. The transition appears to be in the Western style, with CHD as the dominant form of CVD. However, rheumatic heart disease continues to be a major cause of morbidity and mortality. As in South Asia, rheumatic heart disease is also an important cause of CVD morbidity and mortality in sub-Saharan Africa, which largely remains in the first phase of the epidemiologic transition.

Many factors contribute to this heterogeneity among LMICs. First, the regions are in various stages of the epidemiologic transition. Second, vast differences in lifestyle and behavioral risk factors exist. Third, racial and ethnic differences may lead to altered susceptibilities to various forms of CVD. In addition, it should be noted that for most countries in these regions, accurate country-wide data on cause-specific mortality are not complete.

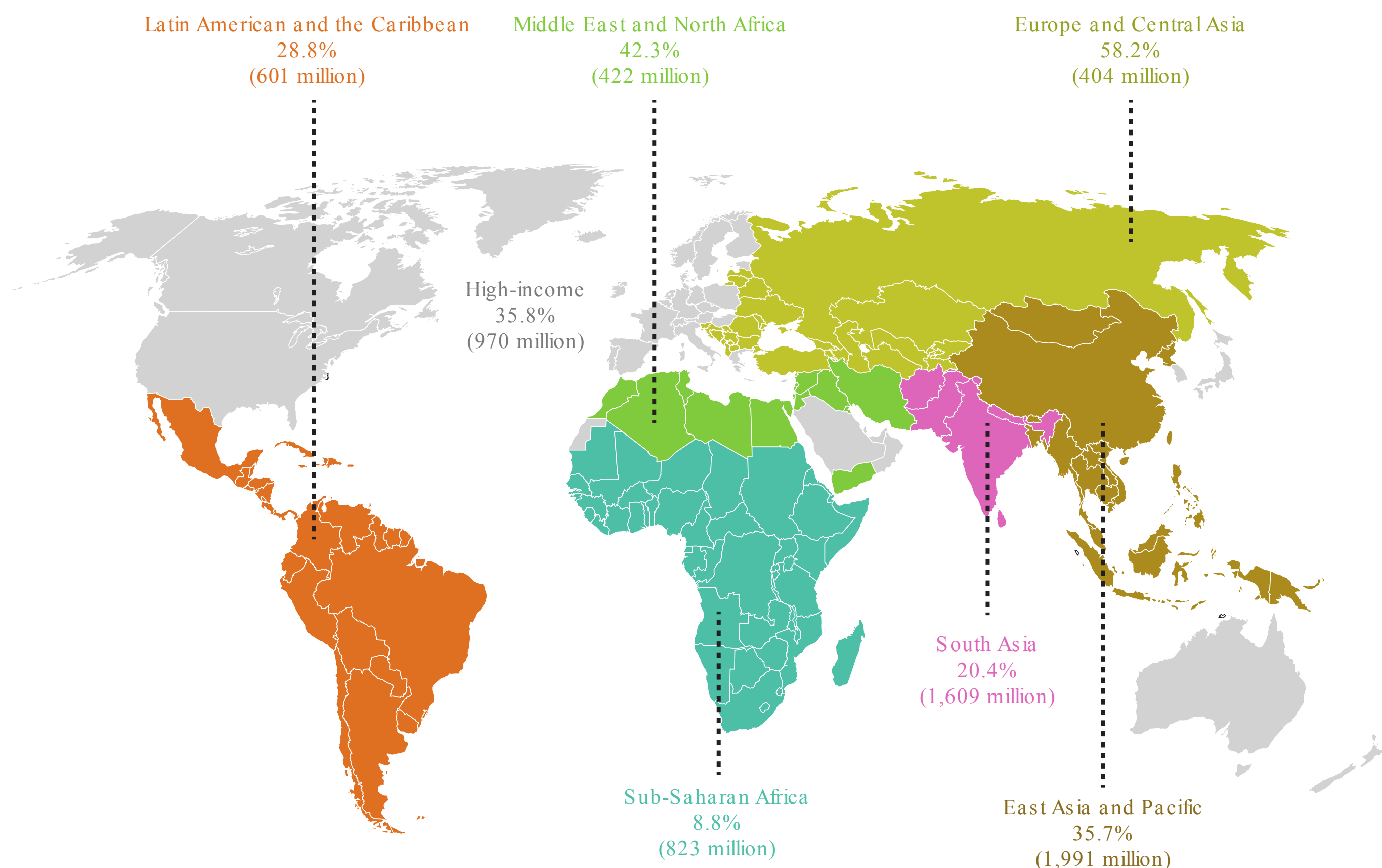


FIGURE 2-2

Cardiovascular disease deaths as a percentage of total deaths and total population in seven economic regions of the world defined by the World Bank. (Based on data from Global Burden of

Disease Study 2010: Global Burden of Disease Study 2010 Mortality Results 1970–2010. Seattle, Institute for Health Metrics and Evaluation, 2012.)

GLOBAL TRENDS IN CARDIOVASCULAR DISEASE

CVD accounts for nearly 30% of deaths worldwide, a number that is expected to increase. In 2010, CHD accounted for 13.3% of all deaths globally and the largest portion of global years of life lost (YLLs) and disability-adjusted life-years (DALYs). The second largest cause of death was stroke (11.1% of all deaths), which was also the third largest contributor to global YLLs and DALYs (Table 2-2). Together, CHD and stroke accounted for nearly a quarter of all deaths worldwide. The burden of stroke is of growing concern among LMICs. The impact of stroke on DALYs and mortality rates is more than three times greater in LMICs as compared to HICs. By 2030, the number of deaths due to stroke is projected to increase by more than 30%, the majority of which will occur in LMICs.

With nearly 85% of the world’s population, LMICs largely drive global CVD rates and trends. Ten million CVD deaths occurred in LMICs in 2010, compared to 5.6 million in HICs. Globally, there is evidence of significant delays in age of occurrence and/or improvements in case fatality rates; between 1990 and 2010, the number of CVD deaths increased by 31%, but age-adjusted death rates decreased by 21.2% in the same period.

TABLE 2-2

MORBIDITY RELATED TO HEART DISEASE: 2010–2030		
DEATHS	2010	BY 2030
CVD deaths: annual number of all deaths	15.6 million	24.2 million
CVD deaths: percentage of all deaths	30.0%	32.5%
CHD deaths: percentage of all male deaths	13.0%	14.9%
CHD deaths: percentage of all female deaths	14.0%	13.1%
Stroke deaths: percentage of all male deaths	9.9%	10.4%
Stroke deaths: percentage of all female deaths	13.0%	11.8%

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease. Source: Adapted from Global Burden of Disease Study 2010: Global Burden of Disease Study 2010 Mortality Results 1970-2010. Seattle, Institute for Health Metrics and Evaluation, 2012; J Mackay, G Mensah: Atlas of Heart Disease and Stroke. Geneva, World Health Organization, 2004.

Although HIC population growth will be fueled by emigration from LMICs, the populations of HICs will shrink as a proportion of the world’s population. The modest decline in CVD death rates that began in the HICs in the latter third of the twentieth century will continue, but the rate of decline appears to be slowing. However, these countries are expected to see an increase in the prevalence of CVD, as well as the absolute number of deaths as the population ages.

Significant portions of the population living in LMICs have entered the third phase of the epidemiologic transition, and some are entering the fourth stage. Changing demographics play a significant role in future predictions for CVD throughout the world. For example, the population growth rate in Eastern Europe and Central Asia was 0.7% in 2012, whereas it was 1.3% in South Asia.

CVD rates will also have an economic impact. Even assuming no increase in CVD risk factors, most countries, but especially India and South Africa, will see a large number of people between 35 and 64 die of CVD over the next 30 years, as well as an increasing level of morbidity among middle-aged people related to heart disease and stroke. In China, it is estimated that there will be 9 million deaths from CVD in 2030—up from 2.4 million in 2002—with half occurring in individuals between 35 and 64 years old.

RISK FACTORS

The global variation in CVD rates is related to temporal and regional variations in known risk behaviors and factors. Ecological analyses of major CVD risk factors and mortality demonstrate high correlations between expected and observed mortality rates for the three main risk factors—smoking, serum cholesterol, and hypertension—and suggest that many of the regional variations are based on differences in conventional risk factors.

BEHAVIORAL RISK FACTORS

Tobacco

Over 1.3 billion people use tobacco worldwide, a number that is projected to increase to 1.6 billion by 2030. Tobacco use currently causes about 5 million deaths annually (9% of all deaths), approximately 1.6 million of which are CVD-related. If current smoking patterns continue, the global burden of disease attributable to tobacco will reach 10 million deaths by 2030. Although tobacco use has been greatest in HICs historically, consumption has shifted dramatically to LMICs in recent decades. Some of the highest tobacco use now occurs

in the East Asia and Pacific region. A unique feature of LMICs is easy access to smoking during the early stages of the epidemiologic transition due to the availability of relatively inexpensive tobacco products. In South Asia, the prominence of other locally produced forms of tobacco besides manufactured cigarettes makes control of consumption more challenging. Secondhand smoke is another well-established cause of CHD, responsible for 600,000 deaths of nonsmokers in 2011. Although smoking bans have both immediate and long-term benefits, implementation varies greatly between countries.

Diet

Total caloric intake per capita increases as countries develop. With regard to CVD, a key element of dietary change is an increase in intake of saturated animal fats and hydrogenated vegetable fats, which contain atherogenic trans fatty acids, along with a decrease in intake of plant-based foods and an increase in simple carbohydrates. Fat contributes less than 20% of calories in rural China and India, less than 30% in Japan, and well above 30% in the United States. Caloric contributions from fat appear to be falling in the HICs. In the United States, between 1971 and 2010, the percentage of calories derived from saturated fat decreased from 13% to 11%.

Physical inactivity

The increased mechanization that accompanies the economic transition leads to a shift from physically demanding, agriculture-based work to largely sedentary industry- and office-based work. In the United States, approximately one-quarter of the population does not participate in any leisure-time physical activity, and only 51.6% of adults report engaging in physical activity three or more times a week. Physical inactivity is similarly high in other regions of the world and is increasing in countries that are rapidly urbanizing as part of their economic transition. In urban China, for example, the proportion of adults who participate in moderate- or high-level activity has decreased significantly, whereas those who participate in low-level activity has increased.

METABOLIC RISK FACTORS

Examination of trends in metabolic risk factors provides insight into changes in the CVD burden globally. Here we describe four metabolic risk factors—lipid levels, hypertension, obesity, and diabetes mellitus—using data from the Global Burden of Disease, Injuries, and Risk Factors Study (GBD 2010). The GBD project identified and compiled mortality and morbidity data from 187 countries from 1980 to 2010.

LIPID LEVELS

Worldwide, high cholesterol levels are estimated to play a role in 56% of ischemic heart disease events and 18% of strokes, amounting to 4.4 million deaths annually. Although mean population plasma cholesterol levels tend to rise as countries move through the epidemiologic transition, mean serum total cholesterol levels have decreased globally between 1980 and 2008 by 0.08 mmol/L per decade in men and 0.07 mmol/L per decade in women. In 2008, age-standardized mean total cholesterol was 4.64 mmol/L (179.4 mg/dL) in men and 4.76 mmol/L (184.2 mg/dL) in women. Large declines occurred in Australasia, North America, and Western Europe (0.19–0.21 mmol/L). Countries in the East Asia and Pacific region experienced increases of greater than 0.08 mmol/L in both men and women. Social and individual changes that accompany urbanization clearly play a role because plasma cholesterol levels tend to be higher among urban residents than among rural residents. This shift is largely driven by greater consumption of dietary fats—primarily from animal products and processed vegetable oils—and decreased physical activity. In HICs, in general, mean population cholesterol levels are falling, whereas wide variation is seen in the LMICs.

HYPERTENSION

Elevated blood pressure is an early indicator of the epidemiologic transition. Worldwide, approximately 62% of strokes and 49% of CHD are attributable to suboptimal (>115 mmHg systolic) blood pressure, which is believed to account for more than 7 million deaths annually. Remarkably, nearly half of this burden occurs among those with systolic blood pressure less than 140 mmHg, even as this level is used at the arbitrary threshold for defining hypertension in many national guidelines. Between 1980 and 2008, the age-standardized prevalence of uncontrolled prevalence has decreased even as the number of people with uncontrolled hypertension has increased. This trend results largely from population growth and aging. Rising mean population blood pressure also occurs as populations industrialize and move from rural to urban settings. For example, the prevalence of hypertension in urban India is 25%, but varies between 10% and 15% in rural communities. One major concern in LMICs is the high rate of undetected, and therefore untreated, hypertension. This may explain, at least in part, the higher stroke rates in these countries in relation to CHD rates during the early stages of the transition. The high rates of hypertension throughout Asia, especially undiagnosed hypertension, likely contribute to the high prevalence of hemorrhagic stroke in the region. Globally, however, mean systolic

blood pressure has decreased among both genders (0.8 mmHg per decade among men; 1.0 mmHg per decade among women).

OBESITY

Although clearly associated with increased risk of CHD, much of the risk posed by obesity may be mediated by other CVD risk factors, including hypertension, diabetes mellitus, and lipid profile imbalances. According to the latest GBD data, nearly 1.46 billion adults were overweight (body mass index ≥ 25 kg/m²) in 2008, and approximately 508 million were obese (BMI ≥ 30 kg/m²). Obesity is increasing throughout the world, particularly in developing countries, where the trajectories are steeper than those experienced by the developed countries. In many of the LMICs, obesity appears to coexist with undernutrition and malnutrition. Adolescents are at particular risk. Currently, 1 in 10 children are estimated to be overweight, a number that is increasing worldwide. Women are also more affected than men, with the number of overweight women generally exceeding underweight women based on data from 36 LMICs.

DIABETES MELLITUS

As a consequence of, or in addition to, increasing body mass index and decreasing levels of physical activity, worldwide rates of diabetes—predominantly type 2 diabetes—are on the rise. According to the most recent data from the GBD project, mean fasting plasma glucose levels have increased globally between 1980 and 2008. An estimated 346 million people worldwide have diabetes. The International Diabetes Foundation predicts that this number will reach 522 million by 2030, a yearly rate of growth that is higher than that of the world's adult population. Nearly 50% of people with diabetes are undiagnosed, and 80% live in LMICs. The highest regional prevalence for diabetes occurs in the Middle East and North Africa, where an estimated 12.5% of the adult population has diabetes. Future growth will also largely occur in this region, along with other LMICs in South Asia and sub-Saharan Africa.

There appear to be clear genetic susceptibilities to diabetes mellitus of various racial and ethnic groups. For example, migration studies suggest that South Asians and Indians tend to be at higher risk than those of European extraction.

SUMMARY

Although CVD rates are declining in the HICs, they are increasing in virtually every other region of the world. The consequences of this preventable epidemic will be substantial on many levels, including individual mortality and morbidity, family suffering, and staggering economic costs.

Three complementary strategies can be used to lessen the impact. First, the overall burden of CVD risk factors can be lowered through population-wide public health measures, such as national campaigns against cigarette smoking, unhealthy diets, and physical inactivity. Second, it is important to identify higher risk subgroups of the population who stand to benefit the most from specific, low-cost prevention interventions, including screening for and treatment of hypertension and elevated cholesterol. Simple, low-cost interventions, such as the “polypill,” a regimen of aspirin, a statin, and an antihypertensive agent, also need to be explored. Third, resources should be allocated to acute as well as secondary prevention interventions. For countries with limited resources, a critical first step in developing a comprehensive plan is better assessment of cause-specific mortality and morbidity, as well as the prevalence of the major preventable risk factors.

In the meantime, the HICs must continue to bear the burden of research and development aimed at prevention and treatment, being mindful of the economic limitations of many countries. The concept of the epidemiologic transition provides insight into how to alter the course of the CVD epidemic. The efficient transfer of low-cost preventive and therapeutic strategies could alter the natural course of this epidemic and thereby reduce the excess global burden of preventable CVD.

CHAPTER 3

APPROACH TO THE PATIENT WITH POSSIBLE CARDIOVASCULAR DISEASE



Joseph Loscalzo

THE MAGNITUDE OF THE PROBLEM

Cardiovascular diseases comprise the most prevalent serious disorders in industrialized nations and are a rapidly growing problem in developing nations (**Chap. 2**). Age-adjusted death rates for coronary heart disease have declined by two-thirds in the last four decades in the United States, reflecting the identification and reduction of risk factors as well as improved treatments and interventions for the management of coronary artery disease, arrhythmias, and heart failure. Nonetheless, cardiovascular diseases remain the most common causes of death, responsible for 35% of all deaths, almost 1 million deaths each year. Approximately one-fourth of these deaths are sudden. In addition, cardiovascular diseases are highly prevalent, diagnosed in 80 million adults, or ~35% of the adult population. The growing prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome (**Chap. 38**), which are important risk factors for atherosclerosis, now threatens to reverse the progress that has been made in the age-adjusted reduction in the mortality rate of coronary heart disease.

For many years cardiovascular disease was considered to be more common in men than in women. In fact, the percentage of all deaths secondary to cardiovascular disease is higher among women (43%) than among men (37%). In addition, although the absolute number of deaths secondary to cardiovascular disease has declined over the past decades in men, this number has actually risen in women. Inflammation, obesity, type 2 diabetes mellitus, and the metabolic syndrome appear to play more prominent roles in the development of coronary atherosclerosis in women than in men. Coronary artery disease (CAD) is more frequently associated with dysfunction of the coronary microcirculation in women than in men. Exercise electrocardiography has a lower diagnostic accuracy in the prediction of epicardial obstruction in women than in men.

NATURAL HISTORY

Cardiovascular disorders often present acutely, as in a previously asymptomatic person who develops an acute myocardial infarction (**Chap. 41**), or a previously asymptomatic patient with hypertrophic cardiomyopathy (**Chap. 27**), or with a prolonged QT interval (**Chap. 18**) whose first clinical manifestation is syncope or even sudden death. However, the alert physician may recognize the patient at risk for these complications long before they occur and often can take measures to prevent their occurrence. For example, a patient with acute myocardial infarction will often have had risk factors for atherosclerosis for many years. Had these risk factors been recognized, their elimination or reduction might have delayed or even prevented the infarction. Similarly, a patient with hypertrophic cardiomyopathy may have had a heart murmur for years and a family history of this disorder. These findings could have led to an echocardiographic examination, recognition of the condition, and appropriate therapy long before the occurrence of a serious acute manifestation.

Patients with valvular heart disease or idiopathic dilated cardiomyopathy, by contrast, may have a prolonged course of gradually increasing dyspnea and other manifestations of chronic heart failure that is punctuated by episodes of acute deterioration only late in the course of the disease. Understanding the natural history of various cardiac disorders is essential for applying appropriate diagnostic and therapeutic measures to each stage of the condition, as well as for providing the patient and family with the likely prognosis.

CARDIAC SYMPTOMS

The symptoms caused by heart disease result most commonly from myocardial ischemia, disturbance of the contraction and/or relaxation of the myocardium,

obstruction to blood flow, or an abnormal cardiac rhythm or rate. Ischemia, which is caused by an imbalance between the heart’s oxygen supply and demand, is manifest most frequently as chest discomfort (**Chap. 4**), whereas reduction of the pumping ability of the heart commonly leads to fatigue and elevated intravascular pressure upstream of the failing ventricle. The latter results in abnormal fluid accumulation, with peripheral edema (**Chap. 7**) or pulmonary congestion and dyspnea (**Chap. 5**). Obstruction to blood flow, as occurs in valvular stenosis, can cause symptoms resembling those of myocardial failure (**Chap. 19**). Cardiac arrhythmias often develop suddenly, and the resulting symptoms and signs—palpitations (**Chap. 8**), dyspnea, hypotension, and syncope (**Chap. 27**)—generally occur abruptly and may disappear as rapidly as they develop.

Although dyspnea, chest discomfort, edema, and syncope are cardinal manifestations of cardiac disease, they occur in other conditions as well. Thus, dyspnea is observed in disorders as diverse as pulmonary disease, marked obesity, and anxiety (**Chap. 5**). Similarly, chest discomfort may result from a variety of noncardiac and cardiac causes other than myocardial ischemia (**Chap. 4**). Edema, an important finding in untreated or inadequately treated heart failure, also may occur with primary renal disease and in hepatic cirrhosis (**Chap. 7**). Syncope occurs not only with serious cardiac arrhythmias but in a number of neurologic conditions as well (**Chap. 27**). Whether heart disease is responsible for these symptoms frequently can be determined by carrying out a careful clinical examination (**Chap. 9**), supplemented by noninvasive testing using electrocardiography at rest and during exercise (**Chap. 11**), echocardiography, roentgenography, and other forms of myocardial imaging (**Chap. 12**).

Myocardial or coronary function that may be adequate at rest may be insufficient during exertion. Thus, dyspnea and/or chest discomfort that appear during activity are characteristic of patients with heart disease, whereas the opposite pattern, i.e., the appearance of these symptoms at rest and their remission during exertion, is rarely observed in such patients. It is important, therefore, to question the patient carefully about the relation of symptoms to exertion.

Many patients with cardiovascular disease may be asymptomatic both at rest and during exertion but may present with an abnormal physical finding such as a heart murmur, elevated arterial pressure, or an abnormality of the electrocardiogram (ECG) or imaging test. It is important to assess the global risk of CAD in asymptomatic individuals, using a combination of clinical assessment and measurement of cholesterol and its fractions, as well as other biomarkers, such as C-reactive protein, in some patients (**Chap. 36**). Since the first clinical manifestation of CAD may be catastrophic—sudden cardiac death, acute myocardial infarction, or stroke in

previous asymptomatic persons—it is mandatory to identify those at high risk of such events and institute further testing and preventive measures.

DIAGNOSIS

As outlined by the New York Heart Association (NYHA), the elements of a complete cardiac diagnosis include the systematic consideration of the following:

- 1. The underlying etiology. Is the disease congenital, hypertensive, ischemic, or inflammatory in origin?
- 2. The anatomic abnormalities. Which chambers are involved? Are they hypertrophied, dilated, or both? Which valves are affected? Are they regurgitant and/or stenotic? Is there pericardial involvement? Has there been a myocardial infarction?
- 3. The physiologic disturbances. Is an arrhythmia present? Is there evidence of congestive heart failure or myocardial ischemia?
- 4. Functional disability. How strenuous is the physical activity required to elicit symptoms? The classification provided by the NYHA has been found to be useful in describing functional disability (**Table 3-1**).

One example may serve to illustrate the importance of establishing a complete diagnosis. In a patient who presents with exertional chest discomfort, the identification of myocardial ischemia as the etiology is of great clinical importance. However, the simple recognition of ischemia is insufficient to formulate a therapeutic strategy or prognosis until the underlying anatomic abnormalities responsible for the myocardial ischemia, e.g., coronary atherosclerosis or aortic stenosis, are identified and a judgment is made about whether other physiologic disturbances that cause an imbalance between myocardial oxygen supply and demand, such as severe anemia,

TABLE 3-1

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION	
Class I	Class III
No limitation of physical activity No symptoms with ordinary exertion	Marked limitation of physical activity Less than ordinary activity causes symptoms Asymptomatic at rest
Class II	Class IV
Slight limitation of physical activity Ordinary activity causes symptoms	Inability to carry out any physical activity without discomfort Symptoms at rest

Source: Modified from The Criteria Committee of the New York Heart Association.

thyrotoxicosis, or supraventricular tachycardia, play contributory roles. Finally, the severity of the disability should govern the extent and tempo of the workup and strongly influence the therapeutic strategy that is selected.

The establishment of a correct and complete cardiac diagnosis usually commences with the history and physical examination (**Chap. 9**). Indeed, the clinical examination remains the basis for the diagnosis of a wide variety of disorders. The clinical examination may then be supplemented by five types of laboratory tests: (1) ECG (**Chap. 11**), (2) noninvasive imaging examinations (chest roentgenogram, echocardiogram, radionuclide imaging, computed tomographic imaging, positron emission tomography, and magnetic resonance imaging) (**Chap. 12**), (3) blood tests to assess risk (e.g., lipid determinations, C-reactive protein [**Chap. 36**]) or cardiac function (e.g., brain natriuretic peptide [BNP] [**Chap. 19**]), (4) occasionally specialized invasive examinations (i.e., cardiac catheterization and coronary arteriography [**Chap. 13**]), and (5) genetic tests to identify monogenic cardiac diseases (e.g., hypertrophic cardiomyopathy [**Chap. 27**], Marfan's syndrome, and abnormalities of cardiac ion channels that lead to prolongation of the QT interval and an increase in the risk of sudden death [**Chap. 17**]). These tests are becoming more widely available.

FAMILY HISTORY

In eliciting the history of a patient with known or suspected cardiovascular disease, particular attention should be directed to the family history. Familial clustering is common in many forms of heart disease. Mendelian transmission of single-gene defects may occur, as in hypertrophic cardiomyopathy (**Chap. 27**), Marfan's syndrome, and sudden death associated with a prolonged QT syndrome (**Chap. 18**). Premature coronary disease and essential hypertension, type 2 diabetes mellitus, and hyperlipidemia (the most important risk factors for CAD) are usually polygenic disorders. Although familial transmission may be less obvious than in the monogenic disorders, it is helpful in assessing risk and prognosis in polygenic disorders, as well. Familial clustering of cardiovascular diseases not only may occur on a genetic basis but also may be related to familial dietary or behavior patterns, such as excessive ingestion of salt or calories and cigarette smoking.

ASSESSMENT OF FUNCTIONAL IMPAIRMENT

When an attempt is made to determine the severity of functional impairment in a patient with heart disease, it is helpful to ascertain the level of activity and the rate at

which it is performed before symptoms develop. Thus, it is not sufficient to state that the patient complains of dyspnea. The breathlessness that occurs after running up two long flights of stairs denotes far less functional impairment than do similar symptoms that occur after taking a few steps on level ground. Also, the degree of customary physical activity at work and during recreation should be considered. The development of two-flight dyspnea in a well-conditioned marathon runner may be far more significant than the development of one-flight dyspnea in a previously sedentary person. The history should include a detailed consideration of the patient's therapeutic regimen. For example, the persistence or development of edema, breathlessness, and other manifestations of heart failure in a patient who is receiving optimal doses of diuretics and other therapies for heart failure (**Chap. 19**) is far graver than are similar manifestations in the absence of treatment. Similarly, the presence of angina pectoris despite treatment with optimal doses of multiple antianginal drugs (**Chap. 39**) is more serious than it is in a patient on no therapy. In an effort to determine the progression of symptoms, and thus the severity of the underlying illness, it may be useful to ascertain what, if any, specific tasks the patient could have carried out 6 months or 1 year earlier that he or she cannot carry out at present.

ELECTROCARDIOGRAM

(See also **Chap. 11**) Although an ECG usually should be recorded in patients with known or suspected heart disease, with the exception of the identification of arrhythmias, conduction abnormalities, ventricular hypertrophy, and acute myocardial infarction, it generally does not establish a specific diagnosis. The range of normal electrocardiographic findings is wide, and the tracing can be affected significantly by many noncardiac factors, such as age, body habitus, and serum electrolyte concentrations. In general, electrocardiographic changes should be interpreted in the context of other abnormal cardiovascular findings.

ASSESSMENT OF THE PATIENT WITH A HEART MURMUR

(**Fig. 3-1**) The cause of a heart murmur can often be readily elucidated from a systematic evaluation of its major attributes: timing, duration, intensity, quality, frequency, configuration, location, and radiation when considered in the light of the history, general physical examination, and other features of the cardiac examination, as described in **Chap. 9**.

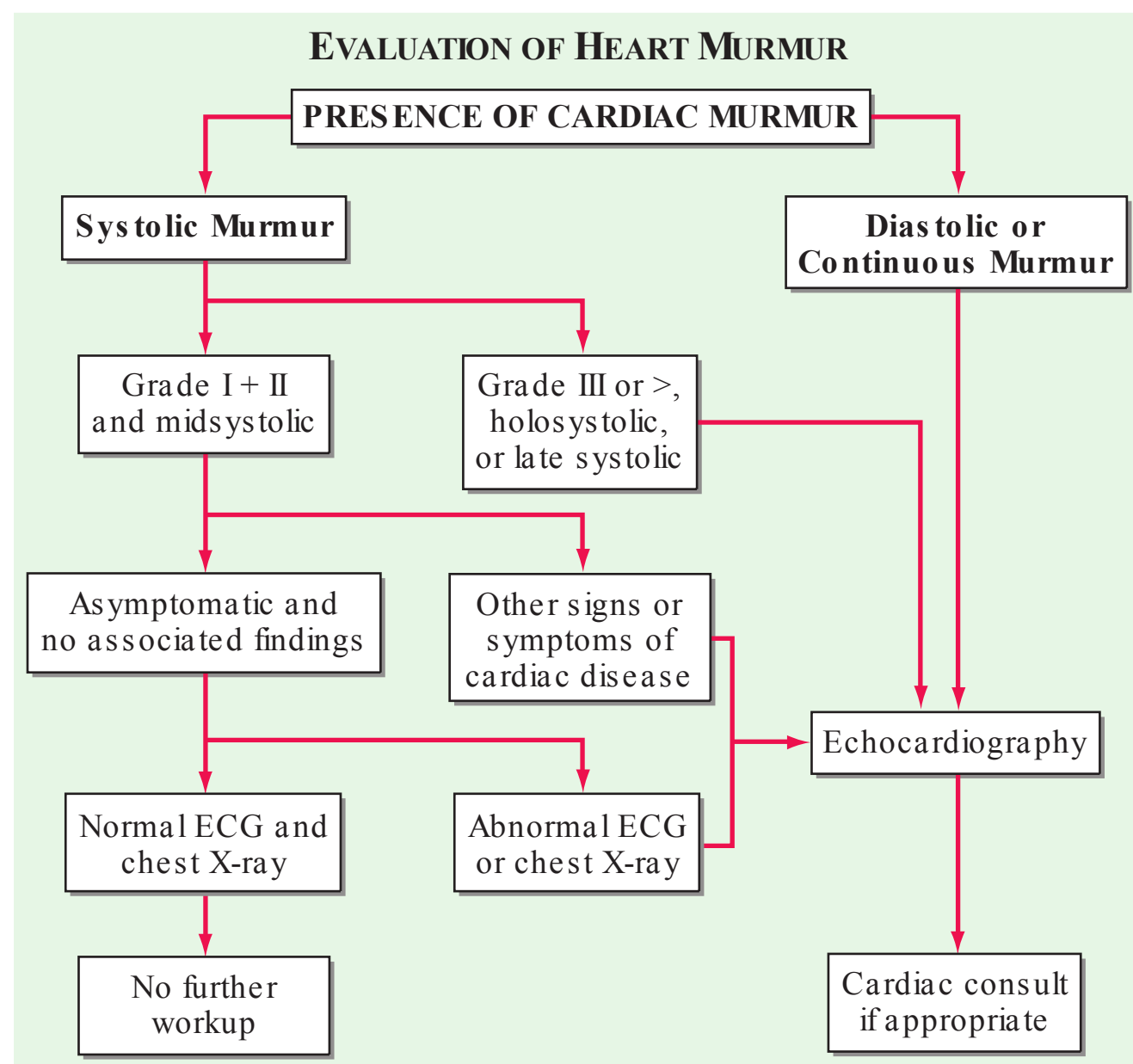


FIGURE 3-1

Approach to the evaluation of a heart murmur. ECG, electrocardiogram. (From RA O'Rourke, in *Primary Cardiology*, 2nd ed, E Braunwald, L Goldman [eds]. Philadelphia, Saunders, 2003.)

The majority of heart murmurs are midsystolic and soft (grades I–II/VI). When such a murmur occurs in an asymptomatic child or young adult without other evidence of heart disease on clinical examination, it is usually benign and echocardiography generally is not required. By contrast, two-dimensional and Doppler echocardiography (**Chap. 12**) are indicated in patients with loud systolic murmurs (grades $\geq$ III/VI), especially those that are holosystolic or late systolic, and in most patients with diastolic or continuous murmurs.

PITFALLS IN CARDIOVASCULAR MEDICINE

Increasing subspecialization in internal medicine and the perfection of advanced diagnostic techniques in cardiology can lead to several undesirable consequences. Examples include the following:

1. Failure by the noncardiologist to recognize important cardiac manifestations of systemic illnesses. For example, the presence of mitral stenosis, patent foramen ovale, and/or transient atrial arrhythmia should be considered in a patient with stroke, or the presence of pulmonary hypertension and cor pulmonale should be considered in a patient with scleroderma or Raynaud's syndrome. A cardiovascular examination should be carried out to identify and estimate the severity of the cardiovascular involvement that accompanies many noncardiac disorders.

2. Failure by the cardiologist to recognize underlying systemic disorders in patients with heart disease. For example, hyperthyroidism should be considered in an elderly patient with atrial fibrillation and unexplained heart failure, and Lyme disease should be considered in a patient with unexplained fluctuating atrioventricular block. A cardiovascular abnormality may provide the clue critical to the recognition of some systemic disorders. For example, an unexplained pericardial effusion may provide an early clue to the diagnosis of tuberculosis or a neoplasm.
3. Overreliance on and overutilization of laboratory tests, particularly invasive techniques, for the evaluation of the cardiovascular system. Cardiac catheterization and coronary arteriography (**Chap. 13**) provide precise diagnostic information that may be crucial in developing a therapeutic plan in patients with known or suspected CAD. Although a great deal of attention has been directed to these examinations, it is important to recognize that they serve to supplement, not supplant, a careful examination carried out with clinical and noninvasive techniques. A coronary arteriogram should not be performed in lieu of a careful history in patients with chest pain suspected of having ischemic heart disease. Although coronary arteriography may establish whether the coronary arteries are obstructed and to what extent, the results of the procedure by themselves often do not provide a definitive answer to the question of whether a patient's complaint of chest discomfort is attributable to coronary atherosclerosis and whether or not revascularization is indicated.

Despite the value of invasive tests in certain circumstances, they entail some small risk to the patient, involve discomfort and substantial cost, and place a strain on medical facilities. Therefore, they should be carried out only if the results can be expected to modify the patient's management.

DISEASE PREVENTION AND MANAGEMENT

The prevention of heart disease, especially of CAD, is one of the most important tasks of primary care health givers as well as cardiologists. Prevention begins with risk assessment, followed by attention to lifestyle, such as achieving optimal weight, physical activity, and smoking cessation, and then aggressive treatment of all abnormal risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus.

After a complete diagnosis has been established in patients with known heart disease, a number of

management options are usually available. Several examples may be used to demonstrate some of the principles of cardiovascular therapeutics:

1. In the absence of evidence of heart disease, the patient should be clearly informed of this assessment and not be asked to return at intervals for repeated examinations. If there is no evidence of disease, such continued attention may lead to the patient's developing inappropriate concern about the possibility of heart disease.
2. If there is no evidence of cardiovascular disease but the patient has one or more risk factors for the development of ischemic heart disease (**Chap. 39**), a plan for their reduction should be developed and the patient should be retested at intervals to assess compliance and efficacy in risk reduction.
3. Asymptomatic or mildly symptomatic patients with valvular heart disease that is anatomically severe should be evaluated periodically, every 6 to 12 months, by clinical and noninvasive examinations. Early signs of deterioration of ventricular function

may signify the need for surgical treatment before the development of disabling symptoms, irreversible myocardial damage, and excessive risk of surgical treatment (**Chap. 23**).

4. In patients with CAD (**Chap. 39**), available practice guidelines should be considered in the decision on the form of treatment (medical, percutaneous coronary intervention, or surgical revascularization). Mechanical revascularization may be employed too frequently in the United States and too infrequently in Eastern Europe and developing nations. The mere presence of angina pectoris and/or the demonstration of critical coronary arterial narrowing at angiography should not reflexively evoke a decision to treat the patient by revascularization. Instead, these interventions should be limited to patients with CAD whose angina has not responded adequately to medical treatment or in whom revascularization has been shown to improve the natural history (e.g., acute coronary syndrome or multivessel CAD with left ventricular dysfunction).

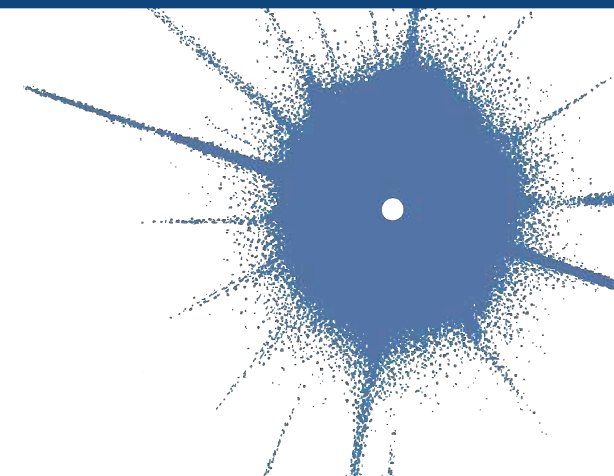
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SECTION II

DIAGNOSIS OF CARDIOVASCULAR DISORDERS

CHAPTER 4

CHEST DISCOMFORT



David A. Morrow

Chest discomfort is among the most common reasons for which patients present for medical attention at either an emergency department (ED) or an outpatient clinic. The evaluation of nontraumatic chest discomfort is inherently challenging owing to the broad variety of possible causes, a minority of which are life-threatening conditions that should not be missed. It is helpful to frame the initial diagnostic assessment and triage of patients with acute chest discomfort around three categories: (1) myocardial ischemia; (2) other cardiopulmonary causes (pericardial disease, aortic emergencies, and pulmonary conditions); and (3) non-cardiopulmonary causes. Although rapid identification of high-risk conditions is a priority of the initial assessment, strategies that incorporate routine liberal use of testing carry the potential for adverse effects of unnecessary investigations.

EPIDEMIOLOGY AND NATURAL HISTORY

Chest discomfort is the third most common reason for visits to the ED in the United States, resulting in 6 to 7 million emergency visits each year. More than 60% of patients with this presentation are hospitalized for further testing, and the rest undergo additional investigation in the ED. Fewer than 25% of evaluated patients are eventually diagnosed with acute coronary syndrome (ACS), with rates of 5–15% in most series of unselected populations. In the remainder, the most common diagnoses are gastrointestinal causes (**Fig. 4-1**), and fewer than 10% are other life-threatening cardiopulmonary conditions. In a large proportion of patients with transient acute chest discomfort, ACS or another acute cardiopulmonary cause is excluded but the cause is not determined. Therefore, the resources and time devoted to the evaluation of chest discomfort in the absence of a severe cause are substantial. Nevertheless, a disconcerting 2–6% of patients with chest discomfort of presumed

non-ischemic etiology who are discharged from the ED are later deemed to have had a missed myocardial infarction (MI). Patients with a missed diagnosis of MI have a 30-day risk of death that is double that of their counterparts who are hospitalized.

The natural histories of ACS, acute pericardial diseases, pulmonary embolism, and aortic emergencies are discussed in **Chaps. 28, 40 and 41, 45, and 46**, respectively. In a study of more than 350,000 patients with unspecified presumed non-cardiopulmonary chest discomfort, the mortality rate 1 year after discharge was <2% and did not differ significantly from age-adjusted mortality in the general population. The estimated rate of major cardiovascular events through 30 days in patients with acute chest pain who had been stratified as low risk was 2.5% in a large population-based study that excluded patients with ST-segment elevation or definite noncardiac chest pain.

CAUSES OF CHEST DISCOMFORT

The major etiologies of chest discomfort are discussed in this section and summarized in **Table 4-1**. Additional elements of the history, physical examination, and diagnostic testing that aid in distinguishing these causes are discussed in a later section (see “Approach to the Patient”).

MYOCARDIAL ISCHEMIA/INJURY

Myocardial ischemia causing chest discomfort, termed angina pectoris, is a primary clinical concern in patients presenting with chest symptoms. Myocardial ischemia is precipitated by an imbalance between myocardial oxygen requirements and myocardial oxygen supply, resulting in insufficient delivery of oxygen to meet the heart’s metabolic demands. Myocardial oxygen consumption may be elevated by increases in heart rate, ventricular wall stress, and myocardial contractility,

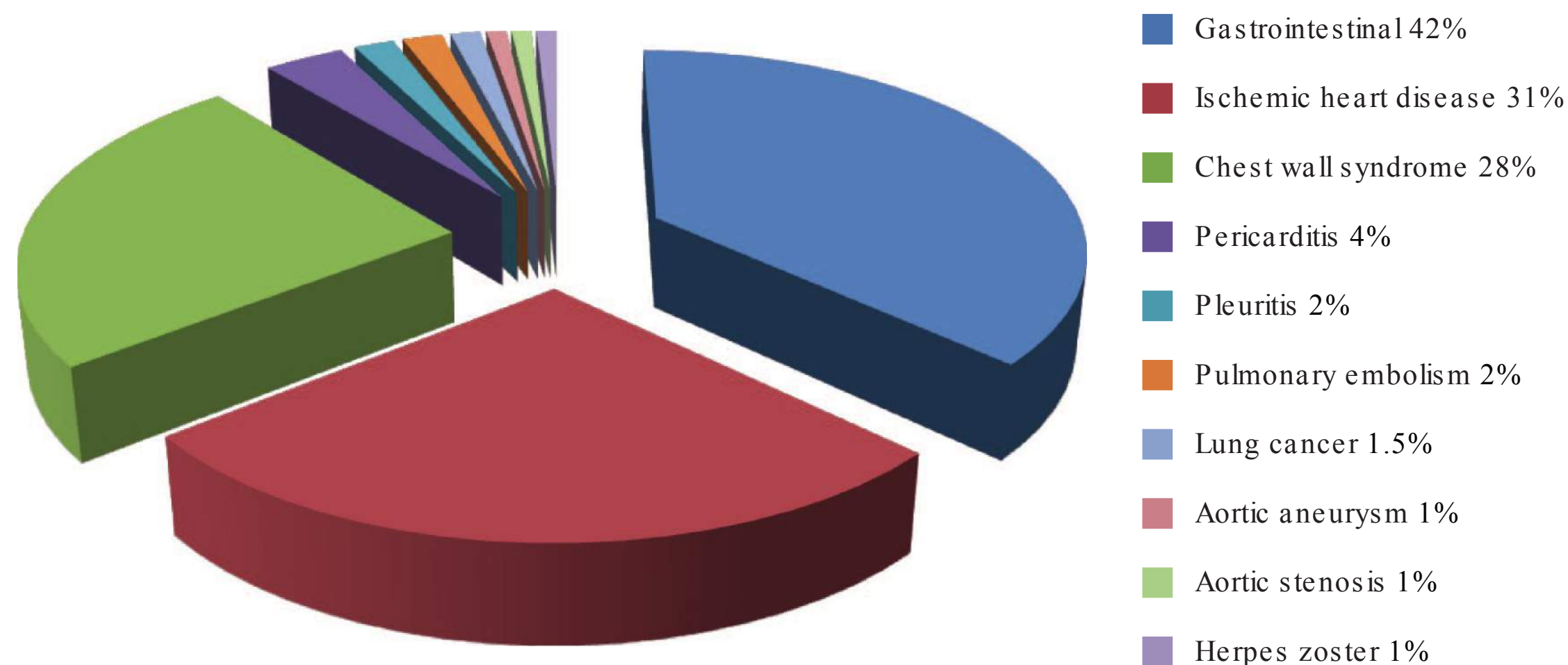


FIGURE 4-1
Distribution of final discharge diagnoses in patients with nontraumatic acute chest pain. (Figure prepared from data in P Fruergaard et al: Eur Heart J 17:1028, 496.)

TABLE 4-1
TYPICAL CLINICAL FEATURES OF MAJOR CAUSES OF ACUTE CHEST DISCOMFORT

SYSTEM	CONDITION	ONSET/DURATION	QUALITY	LOCATION	ASSOCIATED FEATURES
Cardiopulmonary					
Cardiac	Myocardial ischemia	Stable angina: Precipitated by exertion, cold, or stress; 2–10 min Unstable angina: Increasing pattern or at rest Myocardial infarction: Usually >30 min	Pressure, tightness, squeezing, heaviness, burning	Retrosternal; often radiation to neck, jaw, shoulders, or arms; sometimes epigastric	S ₄ gallop or mitral regurgitation murmur (rare) during pain; S ₃ or rales if severe ischemia or complication of myocardial infarction
	Pericarditis	Variable; hours to days; may be episodic	Pleuritic, sharp	Retrosternal or toward cardiac apex; may radiate to left shoulder	May be relieved by sitting up and leaning forward; pericardial friction rub
Vascular	Acute aortic syndrome	Sudden onset of unrelenting pain	Tearing or ripping; knifelike	Anterior chest, often radiating to back, between shoulder blades	Associated with hypertension and/or underlying connective tissue disorder; murmur of aortic insufficiency; loss of peripheral pulses
	Pulmonary embolism	Sudden onset	Pleuritic; may manifest as heaviness with massive pulmonary embolism	Often lateral, on the side of the embolism	Dyspnea, tachypnea, tachycardia, and hypotension
	Pulmonary hypertension	Variable; often exertional	Pressure	Substernal	Dyspnea, signs of increased venous pressure

(continued)

TABLE 4-1
TYPICAL CLINICAL FEATURES OF MAJOR CAUSES OF ACUTE CHEST DISCOMFORT (CONTINUED)

SYSTEM	CONDITION	ONSET/DURATION	QUALITY	LOCATION	ASSOCIATED FEATURES
Pulmonary	Pneumonia or pleuritis	Variable	Pleuritic	Unilateral, often localized	Dyspnea, cough, fever, rales, occasional rub
	Spontaneous pneumothorax	Sudden onset	Pleuritic	Lateral to side of pneumothorax	Dyspnea, decreased breath sounds on side of pneumothorax
Non-cardiopulmonary					
Gastrointestinal	Esophageal reflux	10–60 min	Burning	Substernal, epigastric	Worsened by post-prandial recumbency; relieved by antacids
	Esophageal spasm	2–30 min	Pressure, tightness, burning	Retrosternal	Can closely mimic angina
	Peptic ulcer	Prolonged; 60–90 min after meals	Burning	Epigastric, substernal	Relieved with food or antacids
	Gallbladder disease	Prolonged	Aching or colicky	Epigastric, right upper quadrant; sometimes to the back	May follow meal
Neuromuscular	Costochondritis	Variable	Aching	Sternal	Sometimes swollen, tender, warm over joint; may be reproduced by localized pressure on examination
	Cervical disk disease	Variable; may be sudden	Aching; may include numbness	Arms and shoulders	May be exacerbated by movement of neck
	Trauma or strain	Usually constant	Aching	Localized to area of strain	Reproduced by movement or palpation
	Herpes zoster	Usually prolonged	Sharp or burning	Dermatomal distribution	Vesicular rash in area of discomfort
Psychological	Emotional and psychiatric conditions	Variable; may be fleeting or prolonged	Variable; often manifests as tightness and dyspnea with feeling of panic or doom	Variable; may be retrosternal	Situational factors may precipitate symptoms; history of panic attacks, depression

whereas myocardial oxygen supply is determined by coronary blood flow and coronary arterial oxygen content. When myocardial ischemia is sufficiently severe and prolonged in duration (as little as 20 min), irreversible cellular injury occurs, resulting in MI.

Ischemic heart disease is most commonly caused by atheromatous plaque that obstructs one or more of the epicardial coronary arteries. Stable ischemic heart disease (**Chap. 39**) usually results from the gradual

atherosclerotic narrowing of the coronary arteries. Stable angina is characterized by ischemic episodes that are typically precipitated by a superimposed increase in oxygen demand during physical exertion and relieved upon resting. Ischemic heart disease becomes unstable most commonly when rupture or erosion of one or more atherosclerotic lesions triggers coronary thrombosis (**Chap. 36**). Unstable ischemic heart disease is classified clinically by the presence or absence

of detectable myocardial injury and the presence or absence of ST-segment elevation on the patient's electrocardiogram (ECG). When acute coronary atherothrombosis occurs, the intracoronary thrombus may be partially obstructive, generally leading to myocardial ischemia in the absence of ST-segment elevation. Marked by ischemic symptoms at rest, with minimal activity, or in an accelerating pattern, unstable ischemic heart disease is classified as unstable angina when there is no detectable myocardial injury and as non-ST elevation MI (NSTEMI) when there is evidence of myocardial necrosis (**Chap. 40**). When the coronary thrombus is acutely and completely occlusive, transmural myocardial ischemia usually ensues, with ST-segment elevation on the ECG and myocardial necrosis leading to a diagnosis of ST elevation MI (STEMI, see **Chap. 41**).

Clinicians should be aware that unstable ischemic symptoms may also occur predominantly because of increased myocardial oxygen demand (e.g., during intense psychological stress or fever) or because of decreased oxygen delivery due to anemia, hypoxia, or hypotension. However, the term acute coronary syndrome, which encompasses unstable angina, NSTEMI, and STEMI, is in general reserved for ischemia precipitated by acute coronary atherothrombosis. In order to guide therapeutic strategies, a standardized system for classification of MI has been expanded to discriminate MI resulting from acute coronary thrombosis (type 1) from MI occurring secondary to other imbalances of myocardial oxygen supply and demand (type 2; see **Chap. 40**).

Other contributors to stable and unstable ischemic heart disease, such as endothelial dysfunction, microvascular disease, and vasospasm, may exist alone or in combination with coronary atherosclerosis and may be the dominant cause of myocardial ischemia in some patients. Moreover, non-atherosclerotic processes, including congenital abnormalities of the coronary vessels, myocardial bridging, coronary arteritis, and radiation-induced coronary disease, can lead to coronary obstruction. In addition, conditions associated with extreme myocardial oxygen demand and impaired endocardial blood flow, such as aortic valve disease (**Chap. 46**), hypertrophic cardiomyopathy, or idiopathic dilated cardiomyopathy (**Chap. 27**), can precipitate myocardial ischemia in patients with or without underlying obstructive atherosclerosis.

Characteristics of ischemic chest discomfort

The clinical characteristics of angina pectoris, often referred to simply as “angina,” are highly similar whether the ischemic discomfort is a manifestation of stable ischemic heart disease, unstable angina, or MI; the exceptions are differences in the pattern and duration of symptoms associated with these syndromes (**Table 4-1**). Heberden initially described angina as

a sense of “strangling and anxiety.” Chest discomfort characteristic of myocardial ischemia is typically described as aching, heavy, squeezing, crushing, or constricting. However, in a substantial minority of patients, the quality of discomfort is extremely vague and may be described as a mild tightness, or merely an uncomfortable feeling, that sometimes is experienced as numbness or a burning sensation. The site of the discomfort is usually retrosternal, but radiation is common and generally occurs down the ulnar surface of the left arm; the right arm, both arms, neck, jaw, or shoulders may also be involved. These and other characteristics of ischemic chest discomfort pertinent to discrimination from other causes of chest pain are discussed later in this chapter (see “Approach to the Patient”).

Stable angina usually begins gradually and reaches its maximal intensity over a period of minutes before dissipating within several minutes with rest or with nitroglycerin. The discomfort typically occurs predictably at a characteristic level of exertion or psychological stress. By definition, unstable angina is manifest by self-limited anginal chest discomfort that is exertional but occurs at increased frequency with progressively lower intensity of physical activity or even at rest. Chest discomfort associated with MI is typically more severe, is prolonged (usually lasting ≥ 30 min), and is not relieved by rest.

Mechanisms of cardiac pain

The neural pathways involved in ischemic cardiac pain are poorly understood. Ischemic episodes are thought to excite local chemosensitive and mechanoreceptive receptors that, in turn, stimulate release of adenosine, bradykinin, and other substances that activate the sensory ends of sympathetic and vagal afferent fibers. The afferent fibers traverse the nerves that connect to the upper five thoracic sympathetic ganglia and upper five distal thoracic roots of the spinal cord. From there, impulses are transmitted to the thalamus. Within the spinal cord, cardiac sympathetic afferent impulses may converge with impulses from somatic thoracic structures, and this convergence may be the basis for referred cardiac pain. In addition, cardiac vagal afferent fibers synapse in the nucleus tractus solitarius of the medulla and then descend to the upper cervical spinothalamic tract, and this route may contribute to anginal pain experienced in the neck and jaw.

OTHER CARDIOPULMONARY CAUSES

Pericardial and other myocardial diseases

(See also **Chap. 28**) Inflammation of the pericardium due to infectious or noninfectious causes can be responsible for acute or chronic chest discomfort. The

visceral surface and most of the parietal surface of the pericardium are insensitive to pain. Therefore, the pain of pericarditis is thought to arise principally from associated pleural inflammation and is more common with infectious causes of pericarditis, which typically involve the pleura. Because of this pleural association, the discomfort of pericarditis is usually pleuritic pain that is exacerbated by breathing, coughing, or changes in position. Moreover, owing to the overlapping sensory supply of the central diaphragm via the phrenic nerve with somatic sensory fibers originating in the third to fifth cervical segments, the pain of pleural pericarditis is often referred to the shoulder and neck. Involvement of the pleural surface of the lateral diaphragm can lead to pain in the upper abdomen.

Acute inflammatory and other non-ischemic myocardial diseases can also produce chest discomfort. The symptoms of Takotsubo (stress-related) cardiomyopathy often start abruptly with chest pain and shortness of breath. This form of cardiomyopathy, in its most recognizable form, is triggered by an emotionally or physically stressful event and may mimic acute MI because of its commonly associated ECG abnormalities, including ST-segment elevation, and elevated biomarkers of myocardial injury. Observational studies support a predilection for women >50 years of age. The symptoms of acute myocarditis are highly varied. Chest discomfort may either originate with inflammatory injury of the myocardium or be due to severe increases in wall stress related to poor ventricular performance.

Diseases of the aorta

(See also Chap. 46) Acute aortic dissection (Fig. 4-1) is a less common cause of chest discomfort but is important because of the catastrophic natural history of certain subsets of cases when recognized late or left untreated. Acute aortic syndromes encompass a spectrum of acute aortic diseases related to disruption of the media of the aortic wall. Aortic dissection involves a tear in the aortic intima, resulting in separation of the media and creation of a separate “false” lumen. A penetrating ulcer has been described as ulceration of an aortic atheromatous plaque that extends through the intima and into the aortic media, with the potential to initiate an intramural dissection or rupture into the adventitia. Intramural hematoma is an aortic wall hematoma with no demonstrable intimal flap, no radiologically apparent intimal tear, and no false lumen. Intramural hematoma can occur due to either rupture of the vasa vasorum or, less commonly, a penetrating ulcer.

Each of these subtypes of acute aortic syndrome typically presents with chest discomfort that is often severe, sudden in onset, and sometimes described as “tearing” in quality. Acute aortic syndromes involving the ascending aorta tend to cause pain in the midline of the

anterior chest, whereas descending aortic syndromes most often present with pain in the back. Therefore, dissections that begin in the ascending aorta and extend to the descending aorta tend to cause pain in the front of the chest that extends toward the back, between the shoulder blades. Proximal aortic dissections that involve the ascending aorta (type A in the Stanford nomenclature) are at high risk for major complications that may influence the clinical presentation, including (1) compromise of the aortic ostia of the coronary arteries, resulting in MI; (2) disruption of the aortic valve, causing acute aortic insufficiency; and (3) rupture of the hematoma into the pericardial space, leading to pericardial tamponade.

Knowledge of the epidemiology of acute aortic syndromes can be helpful in maintaining awareness of this relatively uncommon group of disorders (estimated annual incidence, 3 cases per 100,000 population). Nontraumatic aortic dissections are very rare in the absence of hypertension or conditions associated with deterioration of the elastic or muscular components of the aortic media, including pregnancy, bicuspid aortic disease, or inherited connective tissue diseases, such as Marfan and Ehlers-Danlos syndromes.

Although aortic aneurysms are most often asymptomatic, thoracic aortic aneurysms can cause chest pain and other symptoms by compressing adjacent structures. This pain tends to be steady, deep, and occasionally severe. Aortitis, whether of noninfectious or infectious etiology, in the absence of aortic dissection is a rare cause of chest or back discomfort.

Pulmonary conditions

Pulmonary and pulmonary-vascular conditions that cause chest discomfort usually do so in conjunction with dyspnea and often produce symptoms that have a pleuritic nature.

Pulmonary embolism

(See also Chap. 45) Pulmonary emboli (annual incidence, ~1 per 1000) can produce dyspnea and chest discomfort that is sudden in onset. Typically pleuritic in pattern, the chest discomfort associated with pulmonary embolism may result from (1) involvement of the pleural surface of the lung adjacent to a resultant pulmonary infarction; (2) distention of the pulmonary artery; or (3) possibly, right ventricular wall stress and/or subendocardial ischemia related to acute pulmonary hypertension. The pain associated with small pulmonary emboli is often lateral and pleuritic and is believed to be related to the first of these three possible mechanisms. In contrast, massive pulmonary emboli may cause severe substernal pain that may mimic an MI and that is plausibly attributed to the second and third of these potential mechanisms. Massive or submassive

pulmonary embolism may also be associated with syncope, hypotension, and signs of right heart failure. Other typical characteristics that aid in the recognition of pulmonary embolism are discussed later in this chapter (see “Approach to the Patient”).

Pneumothorax

Primary spontaneous pneumothorax is a rare cause of chest discomfort, with an estimated annual incidence in the United States of 7 per 100,000 among men and <2 per 100,000 among women. Risk factors include male sex, smoking, family history, and Marfan syndrome. The symptoms are usually sudden in onset, and dyspnea may be mild; thus, presentation to medical attention is sometimes delayed. Secondary spontaneous pneumothorax may occur in patients with underlying lung disorders, such as chronic obstructive pulmonary disease, asthma, or cystic fibrosis, and usually produces symptoms that are more severe. Tension pneumothorax is a medical emergency caused by trapped intrathoracic air that precipitates hemodynamic collapse.

Other pulmonary parenchymal, pleural, or vascular disease

(See also Chap. 49) Most pulmonary diseases that produce chest pain, including pneumonia and malignancy, do so because of involvement of the pleura or surrounding structures. Pleurisy is typically described as a knife-like pain that is worsened by inspiration or coughing. In contrast, chronic pulmonary hypertension can manifest as chest pain that may be very similar to angina in its characteristics, suggesting right ventricular myocardial ischemia in some cases. Reactive airways diseases similarly can cause chest tightness associated with breathlessness rather than pleurisy.

NON-CARDIOPULMONARY CAUSES

Gastrointestinal conditions

Gastrointestinal disorders are the most common cause of nontraumatic chest discomfort and often produce symptoms that are difficult to discern from more serious causes of chest pain, including myocardial ischemia. Esophageal disorders, in particular, may simulate angina in the character and location of the pain. Gastroesophageal reflux and disorders of esophageal motility are common and should be considered in the differential diagnosis of chest pain (Fig. 4-1 and Table 4-1). Acid reflux often causes a burning discomfort. The pain of esophageal spasm, in contrast, is commonly an intense, squeezing discomfort that is retrosternal in location and, like angina, may be relieved by nitroglycerin or dihydropyridine calcium channel antagonists. Chest pain can also result from

injury to the esophagus, such as a Mallory-Weiss tear or even an esophageal rupture (Boerhaave syndrome) caused by severe vomiting. Peptic ulcer disease is most commonly epigastric in location but can radiate into the chest (Table 4-1).

Hepatobiliary disorders, including cholecystitis and biliary colic, may mimic acute cardiopulmonary diseases. Although the pain arising from these disorders usually localizes to the right upper quadrant of the abdomen, it is variable and may be felt in the epigastrium and radiate to the back and lower chest. The discomfort is sometimes referred to the scapula or may in rare cases be felt in the shoulder, suggesting diaphragmatic irritation. The pain is steady, usually lasts several hours, and subsides spontaneously, without symptoms between attacks. Pain resulting from pancreatitis is typically aching epigastric pain that radiates to the back.

Musculoskeletal and other causes

Chest discomfort can be produced by any musculoskeletal disorder involving the chest wall or the nerves of the chest wall, neck, or upper limbs. Costochondritis causing tenderness of the costochondral junctions (Tietze’s syndrome) is relatively common. Cervical radiculitis may manifest as a prolonged or constant aching discomfort in the upper chest and limbs. The pain may be exacerbated by motion of the neck. Occasionally, chest pain can be caused by compression of the brachial plexus by the cervical ribs, and tendinitis or bursitis involving the left shoulder may mimic the radiation of angina. Pain in a dermatomal distribution can also be caused by cramping of intercostal muscles or by herpes zoster.

Emotional and psychiatric conditions

As many as 10% of patients who present to emergency departments with acute chest discomfort have a panic disorder or related condition (Table 4-1). The symptoms may include chest tightness or aching that is associated with a sense of anxiety and difficulty breathing. The symptoms may be prolonged or fleeting.

APPROACH TO THE PATIENT

Chest Discomfort

Given the broad set of potential causes and the heterogeneous risk of serious complications in patients who present with acute nontraumatic chest discomfort, the priorities of the initial clinical encounter include assessment of (1) the patient’s clinical stability and (2) the probability that the patient has an underlying cause of the discomfort that may be life-threatening. The high-risk conditions of principal concern are acute cardiopulmonary processes,

including ACS, acute aortic syndrome, pulmonary embolism, tension pneumothorax, and pericarditis with tamponade. Among non-cardiopulmonary causes of chest pain, esophageal rupture likely holds the greatest urgency for diagnosis. Patients with these conditions may deteriorate rapidly despite initially appearing well. The remaining population with non-cardiopulmonary conditions has a more favorable prognosis during completion of the diagnostic work-up. A rapid targeted assessment for a serious cardiopulmonary cause is of particular relevance for patients with acute ongoing pain who have presented for emergency evaluation. Among patients presenting in the outpatient setting with chronic pain or pain that has resolved, a general diagnostic assessment is reasonably undertaken (see “Outpatient Evaluation of Chest Discomfort,” below). A series of questions that can be used to structure the clinical evaluation of patients with chest discomfort is shown in [Table 4-2](#).

HISTORY The evaluation of nontraumatic chest discomfort relies heavily on the clinical history and physical examination to direct subsequent diagnostic testing. The evaluating clinician should assess the quality, location (including radiation), and pattern (including onset and duration) of the pain as well as any provoking or alleviating factors. The presence of associated symptoms may also be useful in establishing a diagnosis.

Quality of Pain The quality of chest discomfort alone is never sufficient to establish a diagnosis. However, the characteristics of the pain are pivotal in formulating an initial clinical impression and assessing the likelihood of a serious cardiopulmonary process (Table 4-1), including aortic dissection in particular ([Fig. 4-2](#)). Pressure or tightness is consistent

with a typical presentation of myocardial ischemic pain. Nevertheless, the clinician must remember that some patients with ischemic chest symptoms deny any “pain” but rather complain of dyspnea or a vague sense of anxiety. The severity of the discomfort has poor diagnostic accuracy. It is often helpful to ask about the similarity of the discomfort to previous definite ischemic symptoms. It is unusual for angina to be sharp, as in knifelike, stabbing, or pleuritic; however, patients sometimes use the word “sharp” to convey the intensity of discomfort rather than the quality. Pleuritic discomfort is suggestive of a process involving the pleura, including pericarditis, pulmonary embolism, or pulmonary parenchymal processes. Less frequently, the pain of pericarditis or massive pulmonary embolism is a steady severe pressure or aching that can be difficult to discriminate from myocardial ischemia. “Tearing” or “ripping” pain is often described by patients with acute aortic dissection. However, acute aortic emergencies also present commonly with severe, knifelike pain. A burning quality can suggest acid reflux or peptic ulcer disease but may also occur with myocardial ischemia. Esophageal pain, particularly with spasm, can be a severe squeezing discomfort identical to angina.

Location of Discomfort A substernal location with radiation to the neck, jaw, shoulder, or arms is typical of myocardial ischemic discomfort. Some patients present with aching in sites of radiated pain as their only symptoms of ischemia. However, pain that is highly localized—e.g., that which can be demarcated by the tip of one finger—is highly unusual for angina. A retrosternal location should prompt consideration of esophageal pain; however, other gastrointestinal conditions usually present with pain that is most intense in

TABLE 4-2

CONSIDERATIONS IN THE ASSESSMENT OF THE PATIENT WITH CHEST DISCOMFORT			
1. Could the chest discomfort be due to an acute, potentially life-threatening condition that warrants urgent evaluation and management?			
Unstable ischemic heart disease	Aortic dissection	Pneumothorax	Pulmonary embolism
2. If not, could the discomfort be due to a chronic condition likely to lead to serious complications?			
Stable angina	Aortic stenosis	Pulmonary hypertension	
3. If not, could the discomfort be due to an acute condition that warrants specific treatment?			
Pericarditis	Pneumonia/pleuritis	Herpes zoster	
4. If not, could the discomfort be due to another treatable chronic condition?			
Esophageal reflux		Cervical disk disease	
Esophageal spasm		Arthritis of the shoulder or spine	
Peptic ulcer disease		Costochondritis	
Gallbladder disease		Other musculoskeletal disorders	
Other gastrointestinal conditions		Anxiety state	

Source: Developed by Dr. Thomas H. Lee for the 18th edition of Harrison’s Principles of Internal Medicine.

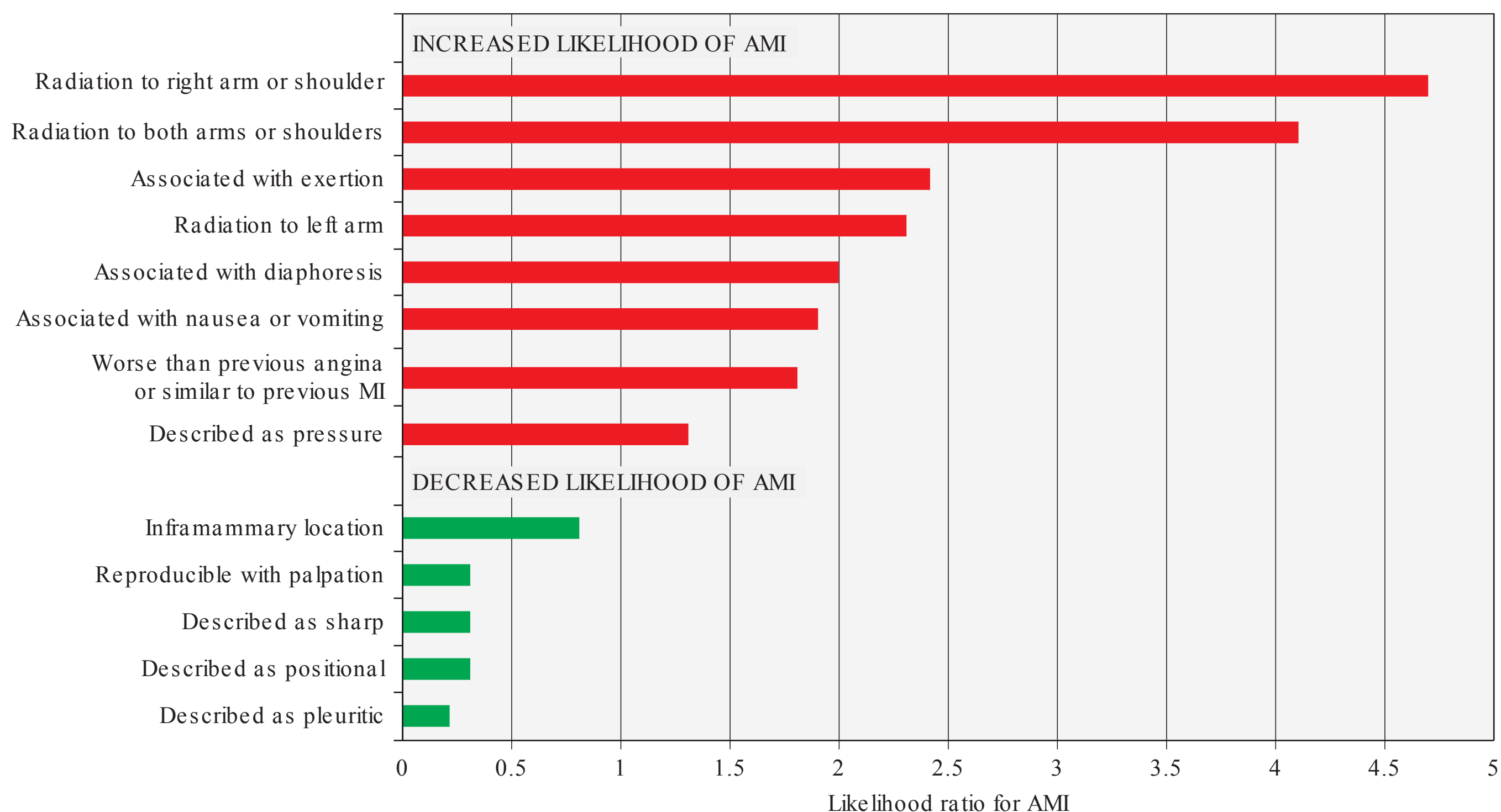


FIGURE 4-2

Association of chest pain characteristics with the probability of acute myocardial infarction (AMI). (Figure prepared from data in CJ Swap, JTNagurney: JAMA294:2623, 2005.)

the abdomen or epigastrium, with possible radiation into the chest. Angina may also occur in an epigastric location. However, pain that occurs solely above the mandible or below the epigastrium is rarely angina. Severe pain radiating to the back, particularly between the shoulder blades, should prompt consideration of an acute aortic syndrome. Radiation to the trapezius ridge is characteristic of pericardial pain and does not usually occur with angina.

Pattern Myocardial ischemic discomfort usually builds over minutes and is exacerbated by activity and mitigated by rest. In contrast, pain that reaches its peak intensity immediately is more suggestive of aortic dissection, pulmonary embolism, or spontaneous pneumothorax. Pain that is fleeting (lasting only a few seconds) is rarely ischemic in origin. Similarly, pain that is constant in intensity for a prolonged period (many hours to days) is unlikely to represent myocardial ischemia if it occurs in the absence of other clinical consequences, such as abnormalities of the ECG, elevation of cardiac biomarkers, or clinical sequelae (e.g., heart failure or hypotension). Both myocardial ischemia and acid reflux may have their onset in the morning, the latter because of the absence of food to absorb gastric acid.

Provoking and Alleviating Factors Patients with myocardial ischemic pain usually prefer to rest, sit, or stop walking. However, clinicians should be aware of the phenomenon of “warm-up angina” in which some patients experience relief of angina as they continue at the same or even a greater

level of exertion without symptoms (**Chap. 39**). Alterations in the intensity of pain with changes in position or movement of the upper extremities and neck are less likely with myocardial ischemia and suggest a musculoskeletal etiology. The pain of pericarditis, however, often is worse in the supine position and relieved by sitting upright and leaning forward. Gastroesophageal reflux may be exacerbated by alcohol, some foods, or by a reclined position. Relief can occur with sitting.

Exacerbation by eating suggests a gastrointestinal etiology such as peptic ulcer disease, cholecystitis, or pancreatitis. Peptic ulcer disease tends to become symptomatic 60–90 min after meals. However, in the setting of severe coronary atherosclerosis, redistribution of blood flow to the splanchnic vasculature after eating can trigger postprandial angina. The discomfort of acid reflux and peptic ulcer disease is usually diminished promptly by acid-reducing therapies. In contrast with its impact in some patients with angina, physical exertion is very unlikely to alter symptoms from gastrointestinal causes of chest pain. Relief of chest discomfort within minutes after administration of nitroglycerin is suggestive of but not sufficiently sensitive or specific for a definitive diagnosis of myocardial ischemia. Esophageal spasm may also be relieved promptly with nitroglycerin. A delay of >10 min before relief is obtained after nitroglycerin suggests that the symptoms either are not caused by ischemia or are caused by severe ischemia, such as during acute MI.

Associated Symptoms Symptoms that accompany myocardial ischemia may include diaphoresis, dyspnea, nausea, fatigue, faintness, and eructations. In addition, these symptoms may exist in isolation as anginal equivalents (i.e., symptoms of myocardial ischemia other than typical angina), particularly in women and the elderly. Dyspnea may occur with multiple conditions considered in the differential diagnosis of chest pain and thus is not discriminative, but the presence of dyspnea is important because it suggests a cardiopulmonary etiology. Sudden onset of significant respiratory distress should lead to consideration of pulmonary embolism and spontaneous pneumothorax. Hemoptysis may occur with pulmonary embolism, or as blood-tinged frothy sputum in severe heart failure but usually points toward a pulmonary parenchymal etiology of chest symptoms. Presentation with syncope or presyncope should prompt consideration of hemodynamically significant pulmonary embolism or aortic dissection as well as ischemic arrhythmias. Although nausea and vomiting suggest a gastrointestinal disorder, these symptoms may occur in the setting of MI (more commonly inferior MI), presumably because of activation of the vagal reflex or stimulation of left ventricular receptors as part of the Bezold-Jarisch reflex.

Past Medical History The past medical history is useful in assessing the patient for risk factors for coronary atherosclerosis (**Chap. 36**) and venous thromboembolism (**Chap. 45**) as well as for conditions that may predispose the patient to specific disorders. For example, a history of connective tissue diseases such as Marfan syndrome should heighten the clinician's suspicion of an acute aortic syndrome or spontaneous pneumothorax. A careful history may elicit clues about depression or prior panic attacks.

PHYSICAL EXAMINATION In addition to providing an initial assessment of the patient's clinical stability, the physical examination of patients with chest discomfort can provide direct evidence of specific etiologies of chest pain (e.g., unilateral absence of lung sounds) and can identify potential precipitants of acute cardiopulmonary causes of chest pain (e.g., uncontrolled hypertension), relevant comorbid conditions (e.g., obstructive pulmonary disease), and complications of the presenting syndrome (e.g., heart failure). However, because the findings on physical examination may be normal in patients with unstable ischemic heart disease, an unremarkable physical exam is not definitively reassuring.

General The patient's general appearance is helpful in establishing an initial impression of the severity of illness. Patients with acute MI or other acute cardiopulmonary disorders often appear anxious, uncomfortable, pale, cyanotic, or diaphoretic. Patients who are massaging or clutching their chests may describe their pain with a clenched fist held against the sternum (Levine's sign). Occasionally, body

habitus is helpful—e.g., in patients with Marfan syndrome or the prototypical young, tall, thin man with spontaneous pneumothorax.

Vital Signs Significant tachycardia and hypotension are indicative of important hemodynamic consequences of the underlying cause of chest discomfort and should prompt a rapid survey for the most severe conditions, such as acute MI with cardiogenic shock, massive pulmonary embolism, pericarditis with tamponade, or tension pneumothorax. Acute aortic emergencies usually present with severe hypertension but may be associated with profound hypotension when there is coronary arterial compromise or dissection into the pericardium. Sinus tachycardia is an important manifestation of submassive pulmonary embolism. Tachypnea and hypoxemia point toward a pulmonary cause. The presence of low-grade fever is nonspecific because it may occur with MI and with thromboembolism in addition to infection.

Pulmonary Examination of the lungs may localize a primary pulmonary cause of chest discomfort, as in cases of pneumonia, asthma, or pneumothorax. Left ventricular dysfunction from severe ischemia/infarction as well as acute valvular complications of MI or aortic dissection can lead to pulmonary edema, which is an indicator of high risk.

Cardiac The jugular venous pulse is often normal in patients with acute myocardial ischemia but may reveal characteristic patterns with pericardial tamponade or acute right ventricular dysfunction (**Chaps. 9 and 28**). Cardiac auscultation may reveal a third or, more commonly, a fourth heart sound, reflecting myocardial systolic or diastolic dysfunction. Murmurs of mitral regurgitation or a harsh murmur of a ventricular-septal defect may indicate mechanical complications of STEMI. A murmur of aortic insufficiency may be a complication of proximal aortic dissection. Other murmurs may reveal underlying cardiac disorders contributory to ischemia (e.g., aortic stenosis or hypertrophic cardiomyopathy). Pericardial friction rubs reflect pericardial inflammation.

Abdominal Localizing tenderness on the abdominal exam is useful in identifying a gastrointestinal cause of the presenting syndrome. Abdominal findings are infrequent with purely acute cardiopulmonary problems, except in the case of underlying chronic cardiopulmonary disease or severe right ventricular dysfunction leading to hepatic congestion.

Vascular Pulse deficits may reflect underlying chronic atherosclerosis, which increases the likelihood of coronary artery disease. However, evidence of acute limb ischemia with loss of the pulse and pallor, particularly in the upper extremities, can indicate catastrophic consequences of aortic dissection. Unilateral lower-extremity swelling should raise suspicion about venous thromboembolism.

Musculoskeletal Pain arising from the costochondral and chondrosternal articulations may be associated with localized swelling, redness, or marked localized tenderness.

Pain on palpation of these joints is usually well localized and is a useful clinical sign, though deep palpation may elicit pain in the absence of costochondritis. Although palpation of the chest wall often elicits pain in patients with various musculoskeletal conditions, it should be appreciated that chest wall tenderness does not exclude myocardial ischemia. Sensory deficits in the upper extremities may be indicative of cervical disk disease.

ELECTROCARDIOGRAPHY Electrocardiography is crucial in the evaluation of nontraumatic chest discomfort. The ECG is pivotal for identifying patients with ongoing ischemia as the principal reason for their presentation as well as secondary cardiac complications of other disorders. Professional society guidelines recommend that an ECG be obtained within 10 min of presentation, with the primary goal of identifying patients with ST-segment elevation diagnostic of MI who are candidates for immediate interventions to restore flow in the occluded coronary artery. ST-segment depression and symmetric T-wave inversions at least 0.2 mV in depth are useful for detecting myocardial ischemia in the absence of STEMI and are also indicative of higher risk of death or recurrent ischemia. Serial performance of ECGs (every 30–60 min) is recommended in the ED evaluation of suspected ACS. In addition, an ECG with right-sided lead placement should be considered in patients with clinically suspected ischemia and a nondiagnostic standard 12-lead ECG. Despite the value of the resting ECG, its sensitivity for ischemia is poor—as low as 20% in some studies.

Abnormalities of the ST segment and T wave may occur in a variety of conditions, including pulmonary embolism, ventricular hypertrophy, acute and chronic pericarditis, myocarditis, electrolyte imbalance, and metabolic disorders. Notably, hyperventilation associated with panic disorder can also lead to nonspecific ST and T-wave abnormalities. Pulmonary embolism is most often associated with sinus tachycardia but can also lead to rightward shift of the ECG axis, manifesting as an S-wave in lead I, with a Q-wave and T-wave in lead III (**Chaps. 11 and 45**). In patients with ST-segment elevation, the presence of diffuse lead involvement not corresponding to a specific coronary anatomic distribution and PR-segment depression can aid in distinguishing pericarditis from acute MI.

CHESTRADIOGRAPHY Plain radiography of the chest is performed routinely when patients present with acute chest discomfort and selectively when individuals who are being evaluated as outpatients have subacute or chronic pain. The chest radiograph is most useful for identifying pulmonary processes, such as pneumonia or pneumothorax. Findings are often unremarkable in patients with ACS, but pulmonary edema may be evident. Other specific findings include widening of the mediastinum in some patients with aortic dissection, Hampton's hump or Westermarck's

sign in patients with pulmonary embolism (**Chap. 45**), or pericardial calcification in chronic pericarditis.

CARDIAC BIOMARKERS Laboratory testing in patients with acute chest pain is focused on the detection of myocardial injury. Such injury can be detected by the presence of circulating proteins released from damaged myocardial cells. Owing to the time necessary for this release, initial biomarkers of injury may be in the normal range, even in patients with STEMI. Because of superior cardiac tissue-specificity compared with creatine kinase MB, cardiac troponin is the preferred biomarker for the diagnosis of MI and should be measured in all patients with suspected ACS at presentation and repeated in 3–6 h. Testing after 6 h is required only when there is uncertainty regarding the onset of pain or when stuttering symptoms have occurred. It is not necessary or advisable to measure troponin in patients without suspicion of ACS unless this test is being used specifically for risk stratification (e.g., in pulmonary embolism or heart failure).

The development of cardiac troponin assays with progressively greater analytical sensitivity has facilitated detection of substantially lower blood concentrations of troponin than was previously possible. This evolution permits earlier detection of myocardial injury, enhances the overall accuracy of a diagnosis of MI, and improves risk stratification in suspected ACS. The greater negative predictive value of a negative troponin result with current-generation assays is an advantage in the evaluation of chest pain in the ED. Rapid rule-out protocols that use serial testing and changes in troponin concentration over as short a period as 1–2 h appear promising and remain under investigation. However, with these advantages has come a trade-off: myocardial injury is detected in a larger proportion of patients who have non-ACS cardiopulmonary conditions than with previous, less sensitive assays. This evolution in testing for myocardial necrosis has rendered other aspects of the clinical evaluation critical to the practitioner's determination of the probability that the symptoms represent ACS. In addition, observation of a change in cardiac troponin concentration between serial samples is useful in discriminating acute causes of myocardial injury from chronic elevation due to underlying structural heart disease, end-stage renal disease, or interfering antibodies. The diagnosis of MI is reserved for acute myocardial injury that is marked by a rising and/or falling pattern—with at least one value exceeding the 99th percentile reference limit—and that is caused by ischemia. Other non-ischemic insults, such as myocarditis, may result in myocardial injury but should not be labeled MI.

Other laboratory assessments may include the d-dimer test to aid in exclusion of pulmonary embolism (**Chap. 45**). Measurement of a B-type natriuretic peptide is useful when considered in conjunction with the clinical history and exam for the diagnosis of heart failure. B-type natriuretic

peptides also provide prognostic information regarding patients with ACS and those with pulmonary embolism. Other putative biomarkers of acute myocardial ischemia or ACS, such as myeloperoxidase, have not been adopted in routine use.

INTEGRATIVE DECISION-AIDS Multiple clinical algorithms have been developed to aid in decision-making during the evaluation and disposition of patients with acute nontraumatic chest pain. Such decision-aids have been derived on the basis of their capacity to estimate either of two closely related but not identical probabilities: (1) the probability of a final diagnosis of ACS and (2) the probability of major cardiac events during short-term follow-up. Such decision-aids are used most commonly to identify patients with a low clinical probability of ACS who are candidates either for early provocative testing for ischemia or for discharge from the ED. Goldman and Lee developed one of the first such decision-aids, using only the ECG and risk indicators—hypotension, pulmonary rales, and known ischemic heart disease—to categorize patients into four risk categories ranging from a <1% to a

>16% probability of a major cardiovascular complication. The Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) combines age, sex, chest pain presence, and ST-segment abnormalities to define a probability of ACS. More recently developed decision-aids are shown in Fig. 4-3. Elements common to each of these tools are (1) symptoms typical for ACS; (2) older age; (3) risk factors for or known atherosclerosis; (4) ischemic ECG abnormalities; and (5) elevated cardiac troponin levels. Although, because of very low specificity, the overall diagnostic performance of such decision-aids is poor (area under the receiver operating curve, 0.55–0.65), they can help identify patients with a very low probability of ACS (e.g., <1%). Nevertheless, no such decision-aid (or single clinical factor) is sufficiently sensitive and well validated to use as a sole tool for clinical decision-making.

Clinicians should differentiate between the algorithms discussed above and risk scores derived for stratification of prognosis (e.g., the TIMI and GRACE risk scores, **Chap. 41**) in patients who already have an established diagnosis of ACS. The latter risk scores were not designed to be used for diagnostic assessment.

HEART Score		
His tory	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Significant ST-depression	2
	Non-specific abnormality	1
	Normal	0
Age	≥65 y	2
	45–<65 y	1
	<45 y	0
Ris k factors	≥3 risk factors	2
	1–2 risk factors	1
	None	0
Troponin (s erial)	≥3 × 99th percentile	2
	1–<3 × 99th percentile	1
	≤99th percentile	0
TOTAL		
Low-ris k: 0–3		
Not low ris k: ≥4		

North American Chest Pain Rule	
High Ris k Criteria	Y/N
Typical symptoms for ischemia	
ECG: acute ischemic changes	
Age ≥50 y	
Known coronary artery disease	
Troponin (serial) >99th percentile	
Low-ris k: All No	
Not Low-ris k: Any Yes	

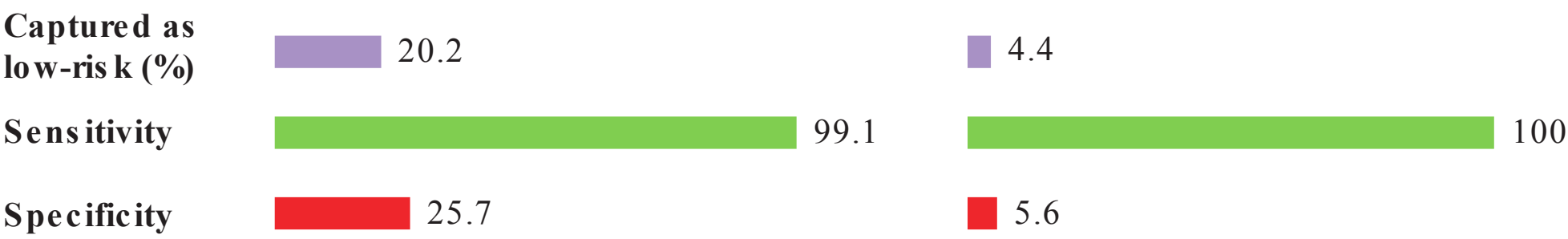


FIGURE 4-3 Examples of decision-aids used in conjunction with serial measurement of cardiac troponin for evaluation of acute chest pain. (Figure prepared from data in SAMahler et al: Int J Cardiol 168:795, 2013.)

PROMOCATIVE TESTING FOR ISCHEMIA Exercise electrocardiography (“stress testing”) is commonly employed for completion of risk stratification of patients who have undergone an initial evaluation that has not revealed a specific cause of chest discomfort and has identified them as being at low or selectively intermediate risk of ACS. Early exercise testing is safe in patients without high-risk findings after 8–12 h of observation and can assist in refining their prognostic assessment. For example, of low-risk patients who underwent exercise testing in the first 48 h after presentation, those without evidence of ischemia had a 2% rate of cardiac events through 6 months, whereas the rate was 15% among patients with either clear evidence of ischemia or an equivocal result. Patients who are unable to exercise may undergo pharmacological stress testing with either nuclear perfusion imaging or echocardiography. Notably, some experts have deemed the routine use of stress testing for low-risk patients unsupported by direct clinical evidence and a potentially unnecessary source of cost.

Professional society guidelines identify ongoing chest pain as a contraindication to stress testing. In selected patients with persistent pain and nondiagnostic ECG and biomarker data, resting myocardial perfusion images can be obtained; the absence of any perfusion abnormality substantially reduces the likelihood of coronary artery disease. In some centers, early myocardial perfusion imaging is performed as part of a routine strategy for evaluating patients at low or intermediate risk of ACS in parallel with other testing. Management of patients with normal perfusion images can be expedited with earlier discharge and outpatient stress testing, if indicated. Those with abnormal rest perfusion imaging, which cannot discriminate between old or new myocardial defects, must undergo additional in-hospital evaluation.

OTHER NONINVASIVE STUDIES Other noninvasive imaging studies of the chest can be used selectively to provide additional diagnostic and prognostic information on patients with chest discomfort.

Echocardiography Echocardiography is not necessarily routine in patients with chest discomfort. However, in patients with an uncertain diagnosis, particularly those with nondiagnostic ST elevation, ongoing symptoms, or hemodynamic instability, detection of abnormal regional wall motion provides evidence of possible ischemic dysfunction. Echocardiography is diagnostic in patients with mechanical complications of MI or in patients with pericardial tamponade. Transthoracic echocardiography is poorly sensitive for aortic dissection, although an intimal flap may sometimes be detected in the ascending aorta.

CT Angiography (See Chap. 12) CT angiography is emerging as a modality for the evaluation of patients with acute chest discomfort. Coronary CT angiography is a sensitive

technique for detection of obstructive coronary disease, particularly in the proximal third of the major epicardial coronary arteries. CT appears to enhance the speed to disposition of patients with a low-intermediate probability for ACS; its major strength being the negative predictive value of a finding of no significant disease. In addition, contrast-enhanced CT can detect focal areas of myocardial injury in the acute setting as decreased areas of enhancement. At the same time, CT angiography can exclude aortic dissection, pericardial effusion, and pulmonary embolism. Balancing factors in the consideration of the emerging role of coronary CT angiography in low-risk patients are radiation exposure and additional testing prompted by nondiagnostic abnormal results.

MRI (See Chap. 12) Cardiac magnetic resonance (CMR) imaging is an evolving, versatile technique for structural and functional evaluation of the heart and the vasculature of the chest. CMR accurately measures ventricular dimensions and function and can be performed as a modality for pharmacologic stress perfusion imaging. Gadolinium-enhanced CMR can provide early detection of MI, defining areas of myocardial necrosis accurately, and can delineate patterns of myocardial disease that are often useful in discriminating ischemic from non-ischemic myocardial injury. Although usually not practical for the urgent evaluation of acute chest discomfort, CMR can be a useful modality for cardiac structural evaluation of patients with elevated cardiac troponin levels in the absence of definite coronary artery disease. CMR coronary angiography is in its early stages. MRI also permits highly accurate assessment for aortic dissection but is infrequently used as the first test because CT and transesophageal echocardiography are usually more practical.

CRITICAL PATHWAYS FOR ACUTE CHEST DISCOMFORT

Because of the challenges inherent in reliably identifying the small proportion of patients with serious causes of acute chest discomfort while not exposing the larger number of low-risk patients to unnecessary testing and extended ED or hospital evaluations, many medical centers have adopted critical pathways to expedite the assessment and management of patients with non-traumatic chest pain, often in dedicated chest pain units. Such pathways are generally aimed at (1) rapid identification, triage, and treatment of high-risk cardiopulmonary conditions (e.g., STEMI); (2) accurate identification of low-risk patients who can be safely observed in units with less intensive monitoring, undergo early exercise testing, or be discharged home; and (3) through more efficient and systematic accelerated diagnostic protocols, safe reduction in costs associated with overuse of testing and unnecessary

hospitalizations. In some studies, provision of protocol-driven care in chest pain units has decreased costs and overall duration of hospital evaluation with no detectable excess of adverse clinical outcomes.

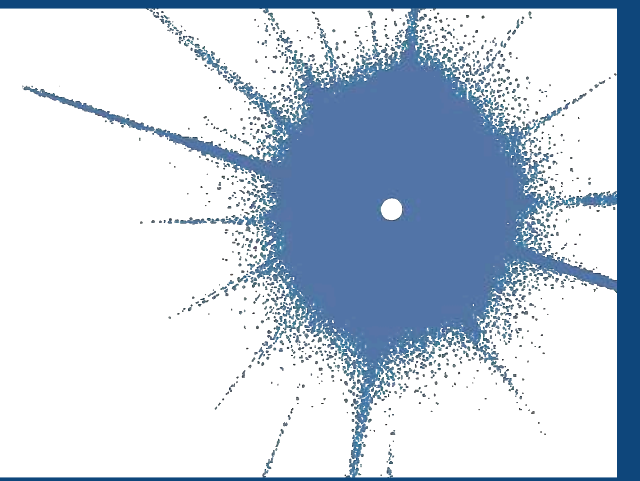
OUTPATIENT EVALUATION OF CHEST DISCOMFORT

Chest pain is common in outpatient practice, with a lifetime prevalence of 20–40% in the general population. More than 25% of patients with MI have had a related visit with a primary care physician in the previous month.

The diagnostic principles are the same as in the ED. However, the pretest probability of an acute cardiopulmonary cause is significantly lower. Therefore, testing paradigms are less intense, with an emphasis on the history, physical examination, and ECG. Moreover, decision-aids developed for settings with a high prevalence of significant cardiopulmonary disease have lower positive predictive value when applied in the practitioner's office. However, in general, if the level of clinical suspicion of ACS is sufficiently high to consider troponin testing, the patient should be referred to the ED for evaluation.

CHAPTER 5

DYSPNEA



Richard M. Schwartzstein

DYSPNEA

The American Thoracic Society defines dyspnea as a “subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors and may induce secondary physiological and behavioral responses.” Dyspnea, a symptom, can be perceived only by the person experiencing it and must be distinguished from the signs of increased work of breathing.

MECHANISMS OF DYSPNEA

Respiratory sensations are the consequence of interactions between the efferent, or outgoing, motor output from the brain to the ventilatory muscles (feed-forward) and the afferent, or incoming, sensory input from receptors throughout the body (feedback) as well as the integrative processing of this information that we infer must be occurring in the brain (Fig. 5-1). In contrast to painful sensations, which can often be attributed to the stimulation of a single nerve ending, dyspnea sensations are more commonly viewed as holistic, more akin to hunger or thirst. A given disease state may lead to dyspnea by one or more mechanisms, some of which may be operative under some circumstances (e.g., exercise) but not others (e.g., a change in position).

Motor efferents

Disorders of the ventilatory pump—most commonly, increased airway resistance or stiffness (decreased compliance) of the respiratory system—are associated with increased work of breathing or the sense of an increased effort to breathe. When the muscles are weak or fatigued, greater effort is required, even though the mechanics of the system are normal. The increased

neural output from the motor cortex is sensed via a corollary discharge, a neural signal that is sent to the sensory cortex at the same time that motor output is directed to the ventilatory muscles.

Sensory afferents

Chemoreceptors in the carotid bodies and medulla are activated by hypoxemia, acute hypercapnia, and acidemia. Stimulation of these receptors and of others that lead to an increase in ventilation produce a sensation of “air hunger.” Mechanoreceptors in the lungs, when stimulated by bronchospasm, lead to a sensation of chest tightness. J-receptors, which are sensitive to interstitial edema, and pulmonary vascular receptors, which are activated by acute changes in pulmonary artery pressure, appear to contribute to air hunger. Hyperinflation is associated with the sensation of increased work of breathing, an inability to get a deep breath, or an unsatisfying breath. Metaboreceptors, which are located in skeletal muscle, are believed to be activated by changes in the local biochemical milieu of the tissue active during exercise and, when stimulated, contribute to breathing discomfort.

Integration: efferent-afferent mismatch

A discrepancy or mismatch between the feed-forward message to the ventilatory muscles and the feedback from receptors that monitor the response of the ventilatory pump increases the intensity of dyspnea. This mismatch is particularly important when there is a mechanical derangement of the ventilatory pump, as in asthma or chronic obstructive pulmonary disease (COPD).

Contribution of emotional or affective factors to dyspnea

Acute anxiety or fear may increase the severity of dyspnea either by altering the interpretation of sensory

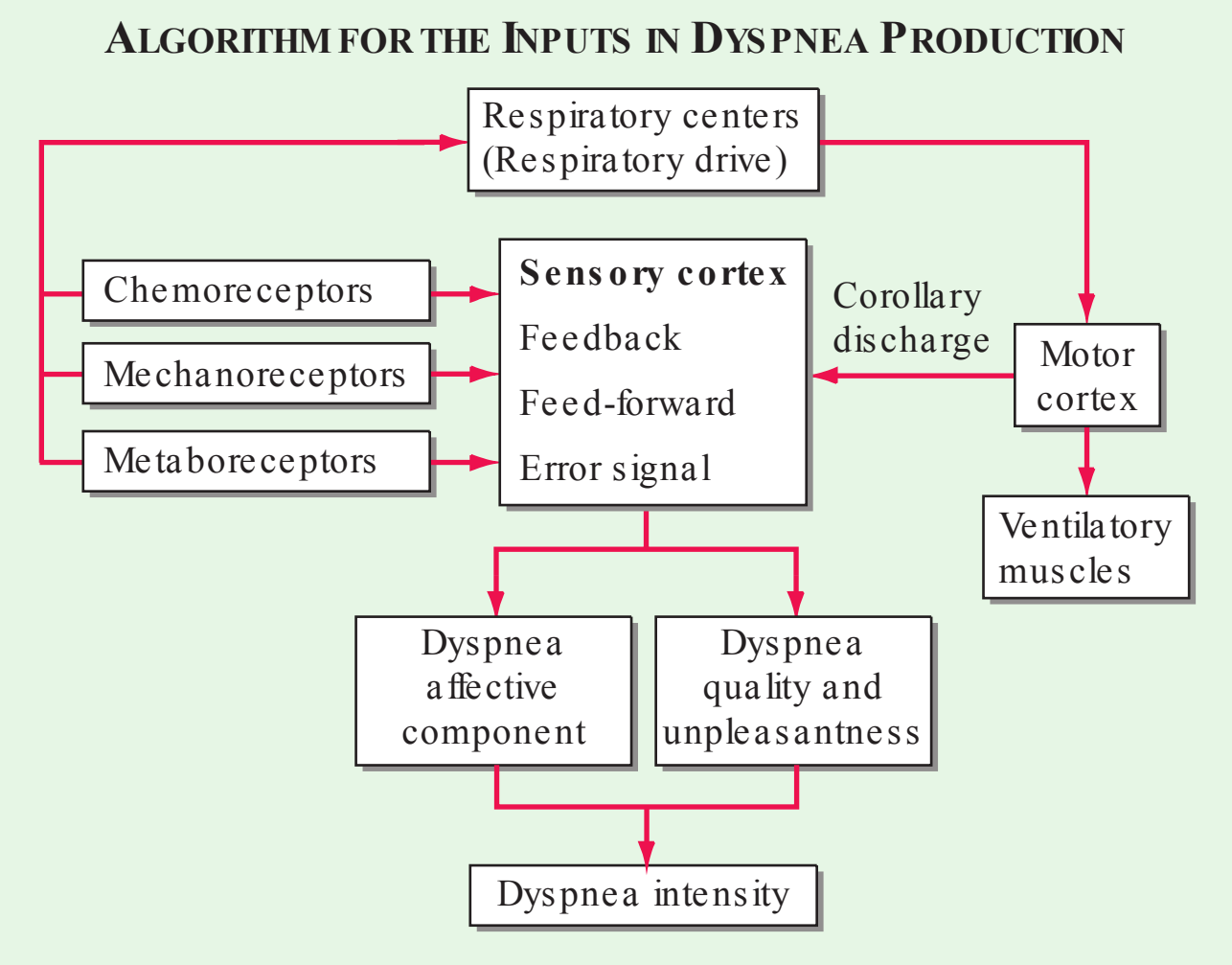


FIGURE 5-1
Hypothetical model for integration of sensory inputs in the production of dyspnea. Afferent information from the receptors throughout the respiratory system projects directly to the sensory cortex to contribute to primary qualitative sensory experiences and to provide feedback on the action of the ventilatory pump. Afferents also project to the areas of the brain responsible for control of ventilation. The motor cortex, responding to input from the control centers, sends neural messages to the ventilatory muscles and a corollary discharge to the sensory cortex (feed-forward with respect to the instructions sent to the muscles). If the feed-forward and feedback messages do not match, an error signal is generated and the intensity of dyspnea increases. An increasing body of data supports the contribution of affective inputs to the ultimate perception of unpleasant respiratory sensations. (Adapted from MA Gillette, RM Schwartzstein, in SH Ahmedzai, MF Muer [eds]. Supportive Care in Respiratory Disease. Oxford, UK, Oxford University Press, 2005.)

data or by leading to patterns of breathing that heighten physiologic abnormalities in the respiratory system. In patients with expiratory flow limitation, for example, the increased respiratory rate that accompanies acute anxiety leads to hyperinflation, increased work and effort of breathing, and the sense of an unsatisfying breath.

ASSESSING DYSPNEA

Quality of sensation

Like pain assessment, dyspnea assessment begins with a determination of the quality of the patient’s discomfort (Table 5-1). Dyspnea questionnaires or lists of phrases commonly used by patients assist those who have difficulty describing their breathing sensations.

Sensory intensity

A modified Borg scale or visual analogue scale can be utilized to measure dyspnea at rest, immediately

TABLE 5-1

ASSOCIATION OF QUALITATIVE DESCRIPTORS, CLINICAL CHARACTERISTICS, AND PATHOPHYSIOLOGIC MECHANISMS OF SHORTNESS OF BREATH		
DESCRIPTOR	CLINICAL EXAMPLES	PATHOPHYSIOLOGY
Chest tightness or constriction	Asthma, CHF	Bronchoconstriction, interstitial edema
Increased work or effort of breathing	COPD, asthma, neuromuscular disease, chest wall restriction	Airway obstruction, neuromuscular disease
“Air hunger,” need to breathe, urge to breathe	CHF, PE, COPD, asthma, pulmonary fibrosis	Increased drive to breathe
Inability to get a deep breath, unsatisfying breath	Moderate to severe asthma and COPD, pulmonary fibrosis, chest wall disease	Hyperinflation and restricted tidal volume
Heavy breathing, rapid breathing, breathing more	Sedentary status in healthy individual or patient with cardiopulmonary disease	Deconditioning

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism.

following exercise, or on recall of a reproducible physical task, such as climbing the stairs at home. An alternative approach is to gain a sense of the patient’s disability by inquiring about what activities are possible. These methods indirectly assess dyspnea and may be affected by nonrespiratory factors, such as leg arthritis or weakness. The Baseline Dyspnea Index and the Chronic Respiratory Disease Questionnaire are commonly used tools for this purpose.

Affective dimension

For a sensation to be reported as a symptom, it must be perceived as unpleasant and interpreted as abnormal. Laboratory studies have demonstrated that air hunger evokes a stronger affective response than does increased effort or work of breathing. Some therapies for dyspnea, such as pulmonary rehabilitation, may reduce breathing discomfort, in part, by altering this dimension.

DIFFERENTIAL DIAGNOSIS

Dyspnea most often results from deviations from normal function in the cardiovascular and respiratory systems. These deviations produce breathlessness as a

consequence of increased drive to breathe; increased effort or work of breathing; and/or stimulation of receptors in the heart, lungs, or vascular system. Most diseases of the respiratory system are associated with alterations in the mechanical properties of the lungs and/or chest wall, and some stimulate pulmonary receptors. In contrast, disorders of the cardiovascular system more commonly lead to dyspnea by causing gas-exchange abnormalities or stimulating pulmonary and/or vascular receptors (Table 5-2).

Respiratory system dyspnea

Diseases of the airways

Asthma and COPD, the most common obstructive lung diseases, are characterized by expiratory airflow obstruction, which typically leads to dynamic hyperinflation of the lungs and chest wall. Patients with moderate to severe disease have both increased resistive and elastic loads (a term that relates to the stiffness of the system) on the ventilatory muscles and experience increased work of breathing. Patients with acute bronchoconstriction also report a sense of tightness, which can exist even when lung function is still within the normal range. These patients are commonly tachypneic; this condition leads to hyperinflation and reduced respiratory system compliance and also limits tidal volume. Both the chest tightness and the tachypnea are probably due to stimulation of pulmonary receptors. Both asthma and COPD may lead to hypoxemia and hypercapnia from ventilation-perfusion ($\dot{V}/Q$) mismatch (and diffusion limitation during exercise with emphysema); hypoxemia is much more common than

hypercapnia as a consequence of the different ways in which oxygen and carbon dioxide bind to hemoglobin.

Diseases of the chest wall

Conditions that stiffen the chest wall, such as kyphoscoliosis, or that weaken ventilatory muscles, such as myasthenia gravis or the Guillain-Barré syndrome, are also associated with an increased effort to breathe. Large pleural effusions may contribute to dyspnea, both by increasing the work of breathing and by stimulating pulmonary receptors if there is associated atelectasis.

Diseases of the lung parenchyma

Interstitial lung diseases, which may arise from infections, occupational exposures, or autoimmune disorders, are associated with increased stiffness (decreased compliance) of the lungs and increased work of breathing. In addition, $\dot{V}/Q$ mismatch and the destruction and/or thickening of the alveolar-capillary interface may lead to hypoxemia and an increased drive to breathe. Stimulation of pulmonary receptors may further enhance the hyperventilation characteristic of mild to moderate interstitial disease.

Cardiovascular system dyspnea

Diseases of the left heart

Diseases of the myocardium resulting from coronary artery disease and nonischemic cardiomyopathies cause a greater left-ventricular end-diastolic volume and an elevation of the left-ventricular end-diastolic as well as pulmonary capillary pressures. These elevated pressures lead to interstitial edema and stimulation of pulmonary receptors, thereby causing dyspnea; hypoxemia due to

TABLE 5-2

MECHANISMS OF DYSPNEA IN COMMON DISEASES

DISEASE	↑ WORK OF BREATHING	↑ DRIVE TO BREATHE	HYPOXEMIA ^a	ACUTE HYPERCAPNIA ^a	STIMULATION OF PULMONARY RECEPTORS	STIMULATION OF VASCULAR RECEPTORS	METABORECEPTORS
COPD	•		•	•			
Asthma	•	•	•	•	•		
ILD	•	•	•	•	•		
PVD		•	•			•	
CPE	•	•	•		•	•	•
NCPE	•	•	•		•		
Anemia							•
Deconditioning							•

^aHypoxemia and hypercapnia are not always present in these conditions. When hypoxemia is present, dyspnea usually persists, albeit at a reduced intensity, with correction of hypoxemia by the administration of supplemental oxygen.

Abbreviations: COPD, chronic obstructive pulmonary disease; CPE, cardiogenic pulmonary edema; ILD, interstitial lung disease; NCPE, noncardiogenic pulmonary edema; PVD, pulmonary vascular disease.

$\dot{V}/Q$ mismatch may also contribute to breathlessness. Diastolic dysfunction, characterized by a very stiff left ventricle, may lead to severe dyspnea with relatively mild degrees of physical activity, particularly if it is associated with mitral regurgitation.

Diseases of the pulmonary vasculature

Pulmonary thromboembolic disease and primary diseases of the pulmonary circulation (primary pulmonary hypertension, pulmonary vasculitis) cause dyspnea via increased pulmonary-artery pressure and stimulation of pulmonary receptors. Hyperventilation is common, and hypoxemia may be present. However, in most cases, use of supplemental oxygen has only a minimal impact on the severity of dyspnea and hyperventilation.

Diseases of the pericardium

Constrictive pericarditis and cardiac tamponade are both associated with increased intracardiac and pulmonary vascular pressures, which are the likely cause of dyspnea in these conditions. To the extent that cardiac output is limited (at rest or with exercise) metaboreceptors may be stimulated if cardiac output is compromised to the degree that lactic acidosis develops; chemoreceptors will also be activated.

Dyspnea with normal respiratory and cardiovascular systems

Mild to moderate anemia is associated with breathing discomfort during exercise. This symptom is thought to be related to stimulation of metaboreceptors; oxygen saturation is normal in patients with anemia. The breathlessness associated with obesity is probably due to multiple mechanisms, including high cardiac output and impaired ventilatory pump function (decreased compliance of the chest wall). Cardiovascular deconditioning (poor fitness) is characterized by the early development of anaerobic metabolism and the stimulation of chemoreceptors and metaboreceptors. Dyspnea that is medically unexplained has been associated with increased sensitivity to the unpleasantness of acute hypercapnia.

APPROACH TO THE PATIENT

Dyspnea History

The patient should be asked to describe in his/her own words what the discomfort feels like as well as the effect of position, infections, and environmental stimuli on the dyspnea (see [Fig. 5-2](#)). Orthopnea is a common indicator of congestive heart failure (CHF), mechanical impairment of the diaphragm associated with obesity, or asthma triggered by esophageal reflux. Nocturnal dyspnea suggests CHF or asthma. Acute, intermittent episodes of dyspnea

are more likely to reflect episodes of myocardial ischemia, bronchospasm, or pulmonary embolism, while chronic persistent dyspnea is typical of COPD, interstitial lung disease, and chronic thromboembolic disease. Information on risk factors for occupational lung disease and for coronary artery disease should be elicited. Left atrial myxoma or hepatopulmonary syndrome should be considered when the patient complains of platypnea—i.e., dyspnea in the upright position with relief in the supine position.

PHYSICAL EXAMINATION The physical examination should begin during the interview of the patient. Inability of the patient to speak in full sentences before stopping to get a deep breath suggests a condition that leads to stimulation of the controller or impairment of the ventilatory pump with reduced vital capacity. Evidence of increased work of breathing (supraclavicular retractions; use of accessory muscles of ventilation; and the tripod position, characterized by sitting with the hands braced on the knees) is indicative of increased airway resistance or stiffness of the lungs and the chest wall. When measuring the vital signs, the physician should accurately assess the respiratory rate and measure the pulsus paradoxus (**Chap. 28**); if the systolic pressure decreases by >10 mmHg, the presence of COPD, acute asthma, or pericardial disease should be considered. During the general examination, signs of anemia (pale conjunctivae), cyanosis, and cirrhosis (spider angiomas, gynecomastia) should be sought. Examination of the chest should focus on symmetry of movement; percussion (dullness is indicative of pleural effusion; hyperresonance is a sign of emphysema); and auscultation (wheezes, rhonchi, prolonged expiratory phase, and diminished breath sounds are clues to disorders of the airways; rales suggest interstitial edema or fibrosis). The cardiac examination should focus on signs of elevated right heart pressures (jugular venous distention, edema, accentuated pulmonic component to the second heart sound); left ventricular dysfunction (S3 and S4 gallops); and valvular disease (murmurs). When examining the abdomen with the patient in the supine position, the physician should note whether there is paradoxical movement of the abdomen: inward motion during inspiration is a sign of diaphragmatic weakness, and rounding of the abdomen during exhalation is suggestive of pulmonary edema. Clubbing of the digits may be an indication of interstitial pulmonary fibrosis, and joint swelling or deformation as well as changes consistent with Raynaud's disease may be indicative of a collagen-vascular process that can be associated with pulmonary disease.

Patients with exertional dyspnea should be asked to walk under observation in order to reproduce the symptoms. The patient should be examined during and at the end of exercise for new findings that were not present at rest and for changes in oxygen saturation.

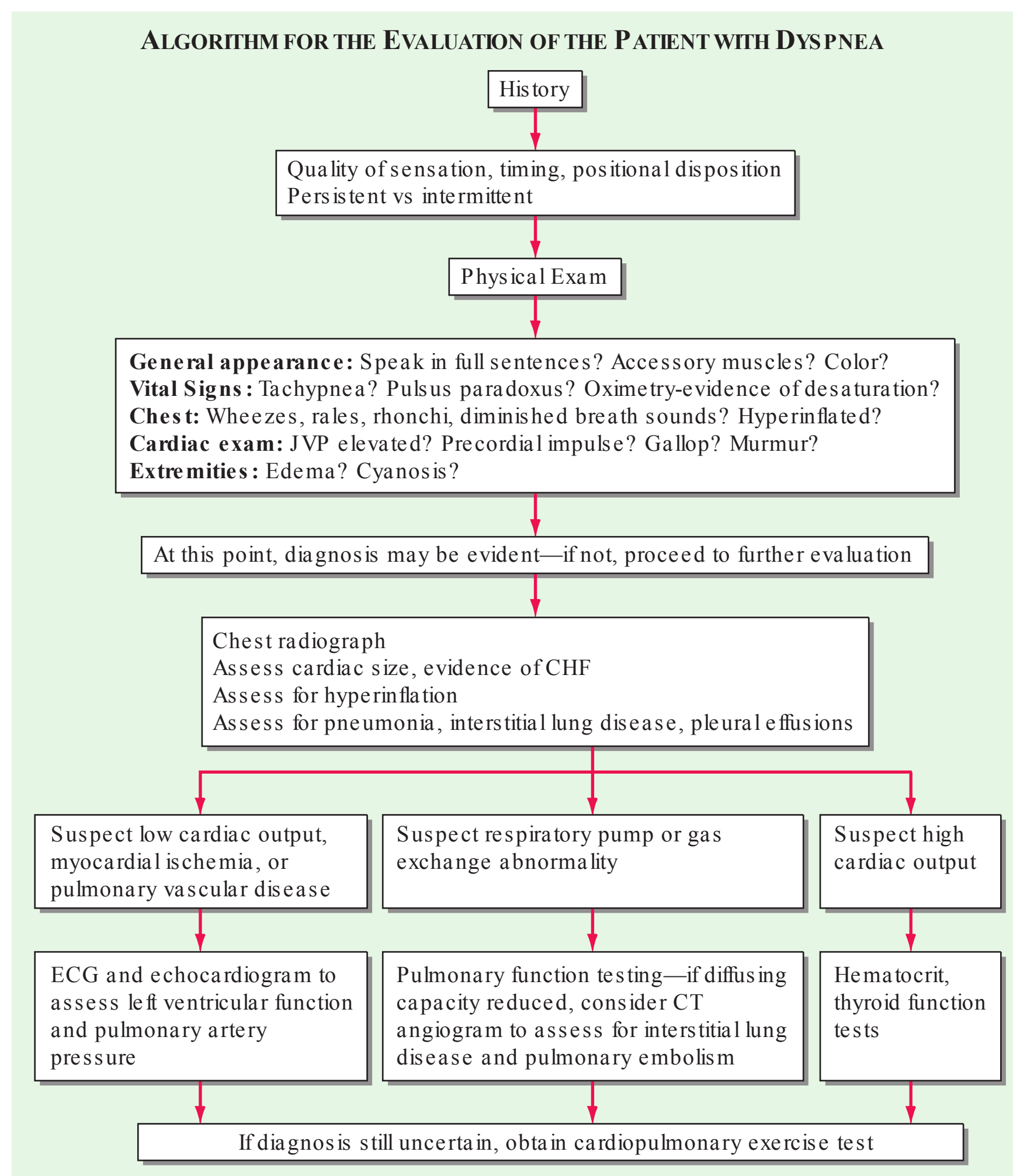


FIGURE 5-2

Algorithm for the evaluation of the patient with dyspnea. JVP, jugular venous pulse; CHF, congestive heart failure; ECG, electrocardiogram; CT, computed tomography. (Adapted from RM

Schwartzstein, D Feller-Kopman, in E Braunwald, L Goldman [eds]. Primary Cardiology, 2nd ed. Philadelphia, WBSaunders, 2003.)

CHEST IMAGING After the history elicitation and the physical examination, a chest radiograph should be obtained. The lung volumes should be assessed: hyperinflation indicates obstructive lung disease, whereas low lung volumes suggest interstitial edema or fibrosis, diaphragmatic dysfunction, or impaired chest wall motion. The pulmonary parenchyma should be examined for evidence of interstitial disease and emphysema. Prominent pulmonary vasculature in the upper zones indicates pulmonary venous hypertension, while enlarged central pulmonary arteries suggest pulmonary arterial hypertension. An enlarged cardiac silhouette suggests dilated cardiomyopathy or valvular disease. Bilateral pleural effusions are typical of CHF and some forms of collagen-vascular disease. Unilateral effusions raise the specter of carcinoma and pulmonary embolism but may also occur in heart failure. CT of the chest is generally reserved for further evaluation of the lung

parenchyma (interstitial lung disease) and possible pulmonary embolism.

LABORATORY STUDIES Laboratory studies should include electrocardiography to seek evidence of ventricular hypertrophy and prior myocardial infarction. Echocardiography is indicated when systolic dysfunction, pulmonary hypertension, or valvular heart disease is suspected. Bronchoprovocation testing is useful in patients with intermittent symptoms suggestive of asthma but normal physical examination and lung function; up to one-third of patients with the clinical diagnosis of asthma do not have reactive airways disease when formally tested. Measurement of brain natriuretic peptide levels in serum is increasingly used to assess for CHF in patients presenting with acute dyspnea but may be elevated in the presence of right ventricular strain as well.

DISTINGUISHING CARDIOVASCULAR FROM RESPIRATORY SYSTEM DYSPNEA If a patient has evidence of both pulmonary and cardiac disease, a cardiopulmonary exercise test should be carried out to determine which system is responsible for the exercise limitation. If, at peak exercise, the patient achieves predicted maximal ventilation, demonstrates an increase in dead space or hypoxemia, or develops bronchospasm, the respiratory system is probably the cause of the problem. Alternatively, if the heart rate is $>85\%$ of the predicted maximum, if the anaerobic threshold occurs early, if the blood pressure becomes excessively high or decreases during exercise, if the O_2 pulse (O_2 consumption/heart rate, an indicator of stroke volume) falls, or if there are ischemic changes on the electrocardiogram, an abnormality of the cardiovascular system is likely the explanation for the breathing discomfort.

TREATMENT Dyspnea

The first goal is to correct the underlying problem responsible for the symptom. If this is not possible, an effort is made to lessen the intensity of the symptom and its effect on the patient's quality of life. Supplemental O_2 should be administered if the resting O_2 saturation is $\leq 89\%$ or if the patient's saturation drops to these levels with activity. For patients with COPD, pulmonary rehabilitation programs have demonstrated positive effects on dyspnea, exercise capacity, and rates of hospitalization. Studies of anxiolytics and antidepressants have not documented consistent benefit. Experimental interventions—e.g., cold air on the face, chest wall vibration, and inhaled furosemide—aimed at modulating the afferent information from receptors throughout the respiratory system are being studied. Morphine has been shown to reduce dyspnea out of proportion to the change in ventilation in laboratory models.

PULMONARY EDEMA

MECHANISMS OF FLUID ACCUMULATION

The extent to which fluid accumulates in the interstitium of the lung depends on the balance of hydrostatic and oncotic forces within the pulmonary capillaries and in the surrounding tissue. Hydrostatic pressure favors movement of fluid from the capillary into the interstitium. The oncotic pressure, which is determined by the protein concentration in the blood, favors movement of fluid into the vessel. Levels of albumin, the primary protein in the plasma, may be low in conditions such as cirrhosis and nephrotic syndrome. While hypoalbuminemia favors movement of fluid into the tissue for any given hydrostatic pressure in the capillary, it is usually

not sufficient by itself to cause interstitial edema. In a healthy individual, the tight junctions of the capillary endothelium are impermeable to proteins, and the lymphatics in the tissue carry away the small amounts of protein that may leak out; together, these factors result in an oncotic force that maintains fluid in the capillary. Disruption of the endothelial barrier, however, allows protein to escape the capillary bed and enhances the movement of fluid into the tissue of the lung.

CARDIOGENIC PULMONARY EDEMA

(See also Chap. 34) Cardiac abnormalities that lead to an increase in pulmonary venous pressure shift the balance of forces between the capillary and the interstitium. Hydrostatic pressure is increased and fluid exits the capillary at an increased rate, resulting in interstitial and, in more severe cases, alveolar edema. The development of pleural effusions may further compromise respiratory system function and contribute to breathing discomfort.

Early signs of pulmonary edema include exertional dyspnea and orthopnea. Chest radiographs show peribronchial thickening, prominent vascular markings in the upper lung zones, and Kerley B lines. As the pulmonary edema worsens, alveoli fill with fluid; the chest radiograph shows patchy alveolar filling, typically in a perihilar distribution, which then progresses to diffuse alveolar infiltrates. Increasing airway edema is associated with rhonchi and wheezes.

NONCARDIOGENIC PULMONARY EDEMA

In noncardiogenic pulmonary edema, lung water increases due to damage of the pulmonary capillary lining with consequent leakage of proteins and other macromolecules into the tissue; fluid follows the protein as oncotic forces are shifted from the vessel to the surrounding lung tissue. This process is associated with dysfunction of the surfactant lining the alveoli, increased surface forces, and a propensity for the alveoli to collapse at low lung volumes. Physiologically, noncardiogenic pulmonary edema is characterized by intrapulmonary shunt with hypoxemia and decreased pulmonary compliance leading to lower functional residual capacity. On pathologic examination, hyaline membranes are evident in the alveoli, and inflammation leading to pulmonary fibrosis may be seen. Clinically, the picture ranges from mild dyspnea to respiratory failure. Auscultation of the lungs may be relatively normal despite chest radiographs that show diffuse alveolar infiltrates. CT scans demonstrate that the distribution of alveolar edema is more heterogeneous than was once thought. Although normal intracardiac pressures are considered by many to be part of the definition of

noncardiogenic pulmonary edema, the pathology of the process, as described above, is distinctly different, and a combination of cardiogenic and noncardiogenic pulmonary edema is observed in some patients.

It is useful to categorize the causes of noncardiogenic pulmonary edema in terms of whether the injury to the lung is likely to result from direct, indirect, or pulmonary vascular causes (**Table 5-3**). Direct injuries are mediated via the airways (e.g., aspiration) or as the consequence of blunt chest trauma. Indirect injury is the consequence of mediators that reach the lung via the bloodstream. The third category includes conditions that may result from acute changes in pulmonary vascular pressures, possibly due to sudden autonomic discharge (in the case of neurogenic and high-altitude pulmonary edema) or sudden swings of pleural pressure as well as transient damage to the pulmonary capillaries (in the case of reexpansion pulmonary edema).

DISTINGUISHING CARDIOGENIC FROM NONCARDIOGENIC PULMONARY EDEMA

The history is essential for assessing the likelihood of underlying cardiac disease as well as for identification of one of the conditions associated with noncardiogenic pulmonary edema. The physical examination in cardiogenic pulmonary edema is notable for evidence of increased intracardiac pressures (S3 gallop, elevated jugular venous pulse, peripheral edema) and rales and/or wheezes on auscultation of the chest. In contrast, the physical examination in noncardiogenic pulmonary edema is dominated by the findings of the precipitating condition; pulmonary findings may be relatively normal in the early stages. The chest radiograph in cardiogenic pulmonary edema typically shows an enlarged cardiac silhouette, vascular redistribution, interstitial thickening, and perihilar alveolar infiltrates; pleural effusions are common. In noncardiogenic pulmonary

TABLE 5-3

COMMON CAUSES OF NONCARDIOGENIC PULMONARY EDEMA

Direct Injury to Lung

Chest trauma, pulmonary contusion
Aspiration
Smoke inhalation
Pneumonia
Oxygen toxicity
Pulmonary embolism, reperfusion

Hematogenous Injury to Lung

Sepsis
Pancreatitis
Nonthoracic trauma
Leukoagglutination reactions
Multiple transfusions
Intravenous drug use (e.g., heroin)
Cardiopulmonary bypass

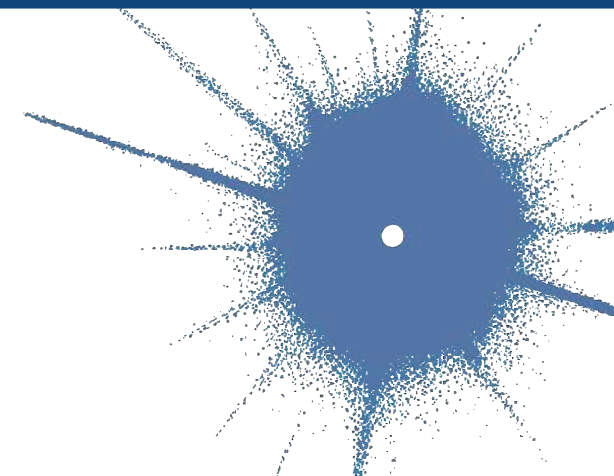
Possible Lung Injury Plus Elevated Hydrostatic Pressures

High-altitude pulmonary edema
Neurogenic pulmonary edema
Reexpansion pulmonary edema

edema, heart size is normal, alveolar infiltrates are distributed more uniformly throughout the lungs, and pleural effusions are uncommon. Finally, the hypoxemia of cardiogenic pulmonary edema is due largely to $\dot{V}/Q$ mismatch and responds to the administration of supplemental oxygen. In contrast, hypoxemia in noncardiogenic pulmonary edema is due primarily to intrapulmonary shunting and typically persists despite high concentrations of inhaled oxygen.

CHAPTER 6

HYPOXIA AND CYANOSIS



Joseph Loscalzo

HYPOXIA

The fundamental purpose of the cardiorespiratory system is to deliver O_2 and nutrients to cells and to remove CO_2 and other metabolic products from them. Proper maintenance of this function depends not only on intact cardiovascular and respiratory systems, but also on an adequate number of red blood cells and hemoglobin and a supply of inspired gas containing adequate O_2 .

RESPONSES TO HYPOXIA

Decreased O_2 availability to cells results in an inhibition of oxidative phosphorylation and increased anaerobic glycolysis. The switch from aerobic to anaerobic metabolism, the Pasteur effect, maintains some, albeit reduced, adenosine 5'-triphosphate (ATP) production. In severe hypoxia, when ATP production is inadequate to meet the energy requirements of ionic and osmotic equilibrium, cell membrane depolarization leads to uncontrolled Ca^{2+} influx and activation of Ca^{2+} -dependent phospholipases and proteases. These events, in turn, cause cell swelling, activation of apoptotic pathways, and, ultimately, cell death.

The adaptations to hypoxia are mediated, in part, by the upregulation of genes encoding a variety of proteins, including glycolytic enzymes, such as phosphoglycerate kinase and phosphofructokinase, as well as the glucose transporters Glut-1 and Glut-2; and by growth factors, such as vascular endothelial growth factor (VEGF) and erythropoietin, which enhance erythrocyte production. The hypoxia-induced increase in expression of these key proteins is governed by the hypoxia-sensitive transcription factor, hypoxia-inducible factor-1 (HIF-1).

During hypoxia, systemic arterioles dilate, at least in part, by opening of K_{ATP} channels in vascular smooth-muscle cells due to the hypoxia-induced reduction in

ATP concentration. By contrast, in pulmonary vascular smooth-muscle cells, inhibition of K^+ channels causes depolarization which, in turn, activates voltage-gated Ca^{2+} channels raising the cytosolic $[Ca^{2+}]$ and causing smooth-muscle cell contraction. Hypoxia-induced pulmonary arterial constriction shunts blood away from poorly ventilated portions toward better ventilated portions of the lung; however, it also increases pulmonary vascular resistance and right ventricular afterload.

Effects on the central nervous system

Changes in the central nervous system (CNS), particularly the higher centers, are especially important consequences of hypoxia. Acute hypoxia causes impaired judgment, motor incoordination, and a clinical picture resembling acute alcohol intoxication. High-altitude illness is characterized by headache secondary to cerebral vasodilation, gastrointestinal symptoms, dizziness, insomnia, fatigue, or somnolence. Pulmonary arterial and sometimes venous constriction causes capillary leakage and high-altitude pulmonary edema (HAPE) (**Chap. 5**), which intensifies hypoxia, further promoting vasoconstriction. Rarely, high-altitude cerebral edema (HACE) develops, which is manifest by severe headache and papilledema and can cause coma. As hypoxia becomes more severe, the regulatory centers of the brainstem are affected, and death usually results from respiratory failure.

Effects on the cardiovascular system

Acute hypoxia stimulates the chemoreceptor reflex arc to induce venoconstriction and systemic arterial vasodilation. These acute changes are accompanied by transiently increased myocardial contractility, which is followed by depressed myocardial contractility with prolonged hypoxia.

CAUSES OF HYPOXIA

Respiratory hypoxia

When hypoxia occurs from respiratory failure, P_{aO_2} declines, and when respiratory failure is persistent, the hemoglobin-oxygen (Hb- O_2) dissociation curve is displaced to the right, with greater quantities of O_2 released at any level of tissue P_{O_2} . Arterial hypoxemia, i.e., a reduction of O_2 saturation of arterial blood (S_{aO_2}), and consequent cyanosis are likely to be more marked when such depression of P_{aO_2} results from pulmonary disease than when the depression occurs as the result of a decline in the fraction of oxygen in inspired air (F_{iO_2}). In this latter situation, P_{aCO_2} falls secondary to anoxia-induced hyperventilation and the Hb- O_2 dissociation curve is displaced to the left, limiting the decline in S_{aO_2} at any level of P_{aO_2} .

The most common cause of respiratory hypoxia is ventilation-perfusion mismatch resulting from perfusion of poorly ventilated alveoli. Respiratory hypoxemia may also be caused by hypoventilation, in which case it is associated with an elevation of P_{aCO_2} . These two forms of respiratory hypoxia are usually correctable by inspiring 100% O_2 for several minutes. A third cause of respiratory hypoxia is shunting of blood across the lung from the pulmonary arterial to the venous bed (intrapulmonary right-to-left shunting) by perfusion of nonventilated portions of the lung, as in pulmonary atelectasis or through pulmonary arteriovenous connections. The low P_{aO_2} in this situation is only partially corrected by an F_{iO_2} of 100%.

Hypoxia secondary to high altitude

As one ascends rapidly to 3000 m (~10,000 ft), the reduction of the O_2 content of inspired air (F_{iO_2}) leads to a decrease in alveolar P_{O_2} to approximately 60 mmHg, and a condition termed high-altitude illness develops (see above). At higher altitudes, arterial saturation declines rapidly and symptoms become more serious; and at 5000 m, unacclimated individuals usually cease to be able to function normally owing to the changes in CNS function described above.

Hypoxia secondary to right-to-left extrapulmonary shunting

From a physiologic viewpoint, this cause of hypoxia resembles intrapulmonary right-to-left shunting but is caused by congenital cardiac malformations, such as tetralogy of Fallot, transposition of the great arteries, and Eisenmenger's syndrome (**Chap. 22**). As in pulmonary right-to-left shunting, the P_{aO_2} cannot be restored to normal with inspiration of 100% O_2 .

Anemic hypoxia

A reduction in hemoglobin concentration of the blood is accompanied by a corresponding decline in the O_2 -carrying capacity of the blood. Although the P_{aO_2} is normal in anemic hypoxia, the absolute quantity of O_2 transported per unit volume of blood is diminished. As the anemic blood passes through the capillaries and the usual quantity of O_2 is removed from it, the P_{O_2} and saturation in the venous blood decline to a greater extent than normal.

Carbon monoxide (CO) intoxication

Hemoglobin that binds with CO (carboxy-hemoglobin, COHb) is unavailable for O_2 transport. In addition, the presence of COHb shifts the Hb- O_2 dissociation curve to the left so that O_2 is unloaded only at lower tensions, further contributing to tissue hypoxia.

Circulatory hypoxia

As in anemic hypoxia, the P_{aO_2} is usually normal, but venous and tissue P_{O_2} values are reduced as a consequence of reduced tissue perfusion and greater tissue O_2 extraction. This pathophysiology leads to an increased arterial-mixed venous O_2 difference (a-v- O_2 difference), or gradient. Generalized circulatory hypoxia occurs in heart failure (**Chap. 19**) and in most forms of shock.

Specific organ hypoxia

Localized circulatory hypoxia may occur as a result of decreased perfusion secondary to arterial obstruction, as in localized atherosclerosis in any vascular bed, or as a consequence of vasoconstriction, as observed in Raynaud's phenomenon (**Chap. 47**). Localized hypoxia may also result from venous obstruction and the resultant expansion of interstitial fluid causing arteriolar compression and, thereby, reduction of arterial inflow. Edema, which increases the distance through which O_2 must diffuse before it reaches cells, can also cause localized hypoxia. In an attempt to maintain adequate perfusion to more vital organs in patients with reduced cardiac output secondary to heart failure or hypovolemic shock, vasoconstriction may reduce perfusion in the limbs and skin, causing hypoxia of these regions.

Increased O_2 requirements

If the O_2 consumption of tissues is elevated without a corresponding increase in perfusion, tissue hypoxia ensues and the P_{O_2} in venous blood declines. Ordinarily, the clinical picture of patients with hypoxia due to an elevated metabolic rate, as in fever or thyrotoxicosis,

is quite different from that in other types of hypoxia: the skin is warm and flushed owing to increased cutaneous blood flow that dissipates the excessive heat produced, and cyanosis is usually absent.

Exercise is a classic example of increased tissue O_2 requirements. These increased demands are normally met by several mechanisms operating simultaneously: (1) increase in the cardiac output and ventilation and, thus, O_2 delivery to the tissues; (2) a preferential shift in blood flow to the exercising muscles by changing vascular resistances in the circulatory beds of exercising tissues, directly and/or reflexly; (3) an increase in O_2 extraction from the delivered blood and a widening of the arteriovenous O_2 difference; and (4) a reduction in the pH of the tissues and capillary blood, shifting the Hb- O_2 curve to the right, and unloading more O_2 from hemoglobin. If the capacity of these mechanisms is exceeded, then hypoxia, especially of the exercising muscles, will result.

Improper oxygen utilization

Cyanide and several other similarly acting poisons cause cellular hypoxia. The tissues are unable to use O_2 , and, as a consequence, the venous blood tends to have a high O_2 tension. This condition has been termed histotoxic hypoxia.

ADAPTATION TO HYPOXIA

An important component of the respiratory response to hypoxia originates in special chemosensitive cells in the carotid and aortic bodies and in the respiratory center in the brainstem. The stimulation of these cells by hypoxia increases ventilation, with a loss of CO_2 , and can lead to respiratory alkalosis. When combined with the metabolic acidosis resulting from the production of lactic acid, the serum bicarbonate level declines.

With the reduction of P_{aO_2} , cerebrovascular resistance decreases and cerebral blood flow increases in an attempt to maintain O_2 delivery to the brain. However, when the reduction of P_{aO_2} is accompanied by hyperventilation and a reduction of P_{aCO_2} , cerebrovascular resistance rises, cerebral blood flow falls, and tissue hypoxia intensifies.

The diffuse, systemic vasodilation that occurs in generalized hypoxia increases the cardiac output. In patients with underlying heart disease, the requirements of peripheral tissues for an increase of cardiac output with hypoxia may precipitate congestive heart failure. In patients with ischemic heart disease, a reduced P_{aO_2} may intensify myocardial ischemia and further impair left ventricular function.

One of the important compensatory mechanisms for chronic hypoxia is an increase in the hemoglobin

concentration and in the number of red blood cells in the circulating blood, i.e., the development of polycythemia secondary to erythropoietin production. In persons with chronic hypoxemia secondary to prolonged residence at a high altitude (>13,000 ft, 4200 m), a condition termed chronic mountain sickness develops. This disorder is characterized by a blunted respiratory drive, reduced ventilation, erythrocytosis, cyanosis, weakness, right ventricular enlargement secondary to pulmonary hypertension, and even stupor.

CYANOSIS

Cyanosis refers to a bluish color of the skin and mucous membranes resulting from an increased quantity of reduced hemoglobin (i.e., deoxygenated hemoglobin) or of hemoglobin derivatives (e.g., methemoglobin or sulfhemoglobin) in the small blood vessels of those tissues. It is usually most marked in the lips, nail beds, ears, and malar eminences. Cyanosis, especially if developed recently, is more commonly detected by a family member than the patient. The florid skin characteristic of polycythemia vera must be distinguished from the true cyanosis discussed here. A cherry-colored flush, rather than cyanosis, is caused by COHb.

The degree of cyanosis is modified by the color of the cutaneous pigment and the thickness of the skin, as well as by the state of the cutaneous capillaries. The accurate clinical detection of the presence and degree of cyanosis is difficult, as proved by oximetric studies. In some instances, central cyanosis can be detected reliably when the SaO_2 has fallen to 85%; in others, particularly in dark-skinned persons, it may not be detected until it has declined to 75%. In the latter case, examination of the mucous membranes in the oral cavity and the conjunctivae rather than examination of the skin is more helpful in the detection of cyanosis.

The increase in the quantity of reduced hemoglobin in the mucocutaneous vessels that produces cyanosis may be brought about either by an increase in the quantity of venous blood as a result of dilation of the venules (including precapillary venules) or by a reduction in the SaO_2 in the capillary blood. In general, cyanosis becomes apparent when the concentration of reduced hemoglobin in capillary blood exceeds 40 g/L (4 g/dL).

It is the absolute, rather than the relative, quantity of reduced hemoglobin that is important in producing cyanosis. Thus, in a patient with severe anemia, the relative quantity of reduced hemoglobin in the venous blood may be very large when considered in relation to the total quantity of hemoglobin in the blood. However, since the concentration of the latter is markedly reduced, the absolute quantity of reduced

hemoglobin may still be low, and, therefore, patients with severe anemia and even marked arterial desaturation may not display cyanosis. Conversely, the higher the total hemoglobin content, the greater the tendency toward cyanosis; thus, patients with marked polycythemia tend to be cyanotic at higher levels of SaO_2 than patients with normal hematocrit values. Likewise, local passive congestion, which causes an increase in the total quantity of reduced hemoglobin in the vessels in a given area, may cause cyanosis. Cyanosis is also observed when nonfunctional hemoglobin, such as methemoglobin (consequential or acquired) or sulfhemoglobin, is present in blood.

Cyanosis may be subdivided into central and peripheral types. In central cyanosis, the SaO_2 is reduced or an abnormal hemoglobin derivative is present, and the mucous membranes and skin are both affected. Peripheral cyanosis is due to a slowing of blood flow and abnormally great extraction of O_2 from normally saturated arterial blood; it results from vasoconstriction and diminished peripheral blood flow, such as occurs in cold exposure, shock, congestive failure, and peripheral vascular disease. Often in these conditions, the mucous membranes of the oral cavity or those beneath the tongue may be spared. Clinical differentiation between central and peripheral cyanosis may not always be simple, and in conditions such as cardiogenic shock with pulmonary edema, there may be a mixture of both types.

DIFFERENTIAL DIAGNOSIS

Central cyanosis

(Table 6-1) Decreased SaO_2 results from a marked reduction in the Pao_2 . This reduction may be brought about by a decline in the Fio_2 without sufficient compensatory alveolar hyperventilation to maintain alveolar PO_2 . Cyanosis usually becomes manifest in an ascent to an altitude of 4000 m (13,000 ft).

Seriously impaired pulmonary function, through perfusion of unventilated or poorly ventilated areas of the lung or alveolar hypoventilation, is a common cause of central cyanosis. This condition may occur acutely, as in extensive pneumonia or pulmonary edema, or chronically, with chronic pulmonary diseases (e.g., emphysema). In the latter situation, secondary polycythemia is generally present and clubbing of the fingers (see below) may occur. Another cause of reduced SaO_2 is shunting of systemic venous blood into the arterial circuit. Certain forms of congenital heart disease are associated with cyanosis on this basis (see above and Chap. 22).

Pulmonary arteriovenous fistulae may be congenital or acquired, solitary or multiple, microscopic or massive. The severity of cyanosis produced by these fistulae depends on their size and number. They occur with

TABLE 6-1

CAUSES OF CYANOSIS

Central Cyanosis

Decreased arterial oxygen saturation

Decreased atmospheric pressure—high altitude

Impaired pulmonary function

Alveolar hypoventilation

Inhomogeneity in pulmonary ventilation and perfusion (perfusion of hypoventilated alveoli)

Impaired oxygen diffusion

Anatomic shunts

Certain types of congenital heart disease

Pulmonary arteriovenous fistulas

Multiple small intrapulmonary shunts

Hemoglobin with low affinity for oxygen

Hemoglobin abnormalities

Methemoglobinemia—hereditary, acquired

Sulfhemoglobinemia—acquired

Carboxyhemoglobinemia (not true cyanosis)

Peripheral Cyanosis

Reduced cardiac output

Cold exposure

Redistribution of blood flow from extremities

Arterial obstruction

Venous obstruction

some frequency in hereditary hemorrhagic telangiectasia. SaO_2 reduction and cyanosis may also occur in some patients with cirrhosis, presumably as a consequence of pulmonary arteriovenous fistulae or portal vein–pulmonary vein anastomoses.

In patients with cardiac or pulmonary right-to-left shunts, the presence and severity of cyanosis depend on the size of the shunt relative to the systemic flow as well as on the Hb- O_2 saturation of the venous blood. With increased extraction of O_2 from the blood by the exercising muscles, the venous blood returning to the right side of the heart is more unsaturated than at rest, and shunting of this blood intensifies the cyanosis. Secondary polycythemia occurs frequently in patients in this setting and contributes to the cyanosis.

Cyanosis can be caused by small quantities of circulating methemoglobin (Hb Fe^{3+}) and by even smaller quantities of sulfhemoglobin; both of these hemoglobin derivatives impair oxygen delivery to the tissues. Although they are uncommon causes of cyanosis, these abnormal hemoglobin species should be sought by spectroscopy when cyanosis is not readily explained by malfunction of the circulatory or respiratory systems. Generally, digital clubbing does not occur with them.

Peripheral cyanosis

Probably the most common cause of peripheral cyanosis is the normal vasoconstriction resulting from exposure to cold air or water. When cardiac output is reduced, cutaneous vasoconstriction occurs as a compensatory mechanism so that blood is diverted from the skin to more vital areas such as the CNS and heart, and cyanosis of the extremities may result even though the arterial blood is normally saturated.

Arterial obstruction to an extremity, as with an embolus, or arteriolar constriction, as in cold-induced vasospasm (Raynaud's phenomenon) (**Chap. 47**), generally results in pallor and coldness, and there may be associated cyanosis. Venous obstruction, as in thrombophlebitis or deep venous thrombosis, dilates the subpapillary venous plexuses and thereby intensifies cyanosis.

APPROACH TO THE PATIENT:

Cyanosis

Certain features are important in arriving at the cause of cyanosis:

1. It is important to ascertain the time of onset of cyanosis. Cyanosis present since birth or infancy is usually due to congenital heart disease.
2. Central and peripheral cyanosis must be differentiated. Evidence of disorders of the respiratory or cardiovascular systems is helpful. Massage or gentle warming of a cyanotic extremity will increase peripheral blood flow and abolish peripheral, but not central, cyanosis.
3. The presence or absence of clubbing of the digits (see below) should be ascertained. The combination of cyanosis and clubbing is frequent in patients with congenital heart disease and right-to-left shunting and is seen occasionally in patients with pulmonary disease, such as lung abscess or pulmonary arteriovenous fistulae. In contrast, peripheral cyanosis or acutely developing central cyanosis is not associated with clubbed digits.

4. Pao_2 and Sao_2 should be determined, and, in patients with cyanosis in whom the mechanism is obscure, spectroscopic examination of the blood should be performed to look for abnormal types of hemoglobin (critical in the differential diagnosis of cyanosis).

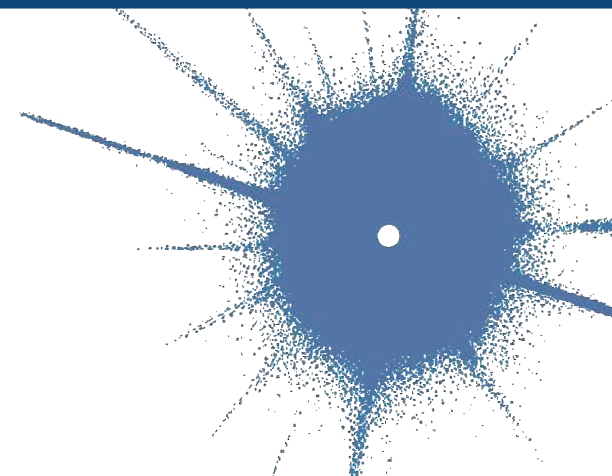
CLUBBING

The selective bulbous enlargement of the distal segments of the fingers and toes due to proliferation of connective tissue, particularly on the dorsal surface, is termed clubbing; there is also increased sponginess of the soft tissue at the base of the clubbed nail. Clubbing may be hereditary, idiopathic, or acquired and associated with a variety of disorders, including cyanotic congenital heart disease (see above), infective endocarditis, and a variety of pulmonary conditions (among them primary and metastatic lung cancer, bronchiectasis, asbestosis, sarcoidosis, lung abscess, cystic fibrosis, tuberculosis, and mesothelioma), as well as with some gastrointestinal diseases (including inflammatory bowel disease and hepatic cirrhosis). In some instances, it is occupational, e.g., in jackhammer operators.

Clubbing in patients with primary and metastatic lung cancer, mesothelioma, bronchiectasis, or hepatic cirrhosis may be associated with hypertrophic osteoarthropathy. In this condition, the subperiosteal formation of new bone in the distal diaphyses of the long bones of the extremities causes pain and symmetric arthritis-like changes in the shoulders, knees, ankles, wrists, and elbows. The diagnosis of hypertrophic osteoarthropathy may be confirmed by bone radiograph or magnetic resonance imaging (MRI). Although the mechanism of clubbing is unclear, it appears to be secondary to humoral substances that cause dilation of the vessels of the distal digits as well as growth factors released from platelet precursors in the digital circulation. In certain circumstances, clubbing is reversible, such as following lung transplantation for cystic fibrosis.

CHAPTER 7

EDEMA



Eugene Braunwald ■ Joseph Loscalzo

STARLING FORCES AND FLUID EXCHANGE

About one-third of total-body water is confined to the extracellular space. Approximately 75% of the latter is interstitial fluid, and the remainder is the plasma. The forces that regulate the disposition of fluid between these two components of the extracellular compartment frequently are referred to as the Starling forces. The hydrostatic pressure within the capillaries and the colloid oncotic pressure in the interstitial fluid tend to promote movement of fluid from the vascular to the extravascular space. By contrast, the colloid oncotic pressure contributed by plasma proteins and the hydrostatic pressure within the interstitial fluid promote the movement of fluid into the vascular compartment. As a consequence, there is movement of water and diffusible solutes from the vascular space at the arteriolar end of the capillaries. Fluid is returned from the interstitial space into the vascular system at the venous end of the capillaries and by way of the lymphatics. These movements are usually balanced so that there is a steady state in the sizes of the intravascular and interstitial compartments, yet a large exchange between them occurs. However, if either the capillary hydrostatic pressure is increased and/or the oncotic pressure is reduced, a further net movement of fluid from intravascular to the interstitial spaces will take place.

Edema is defined as a clinically apparent increase in the interstitial fluid volume, which develops when Starling forces are altered so that there is increased flow of fluid from the vascular system into the interstitium. Edema due to an increase in capillary pressure may result from an elevation of venous pressure caused by obstruction to venous and/or lymphatic drainage. An increase in capillary pressure may be generalized, as occurs in heart failure, or it may be localized to one extremity when venous pressure is elevated due to unilateral thrombophlebitis (see below). The Starling forces

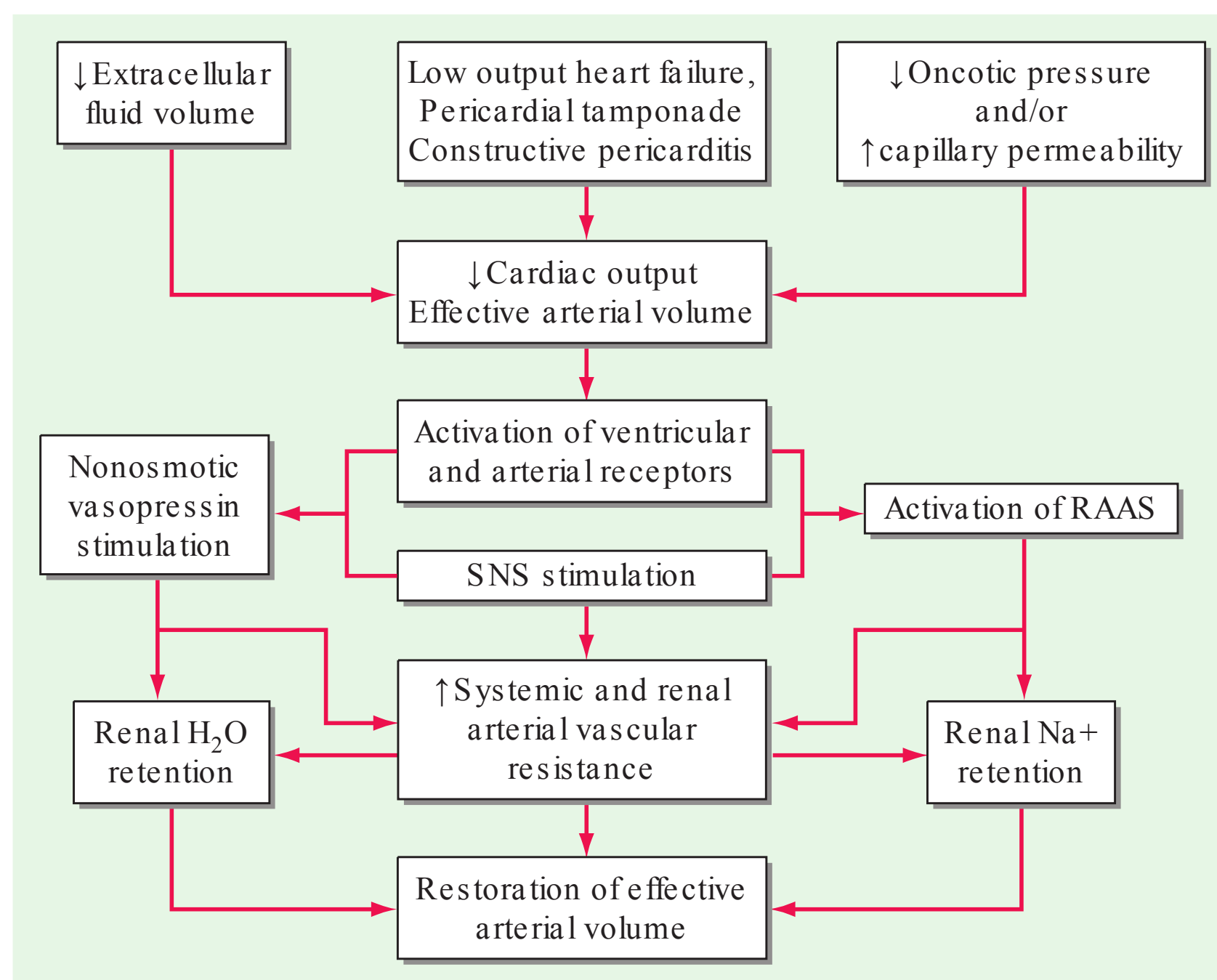
also may be imbalanced when the colloid oncotic pressure of the plasma is reduced owing to any factor that may induce hypoalbuminemia, as when large quantities of protein are lost in the urine such as in the nephrotic syndrome (see below), or when synthesis is reduced in a severe catabolic state.

CAPILLARY DAMAGE

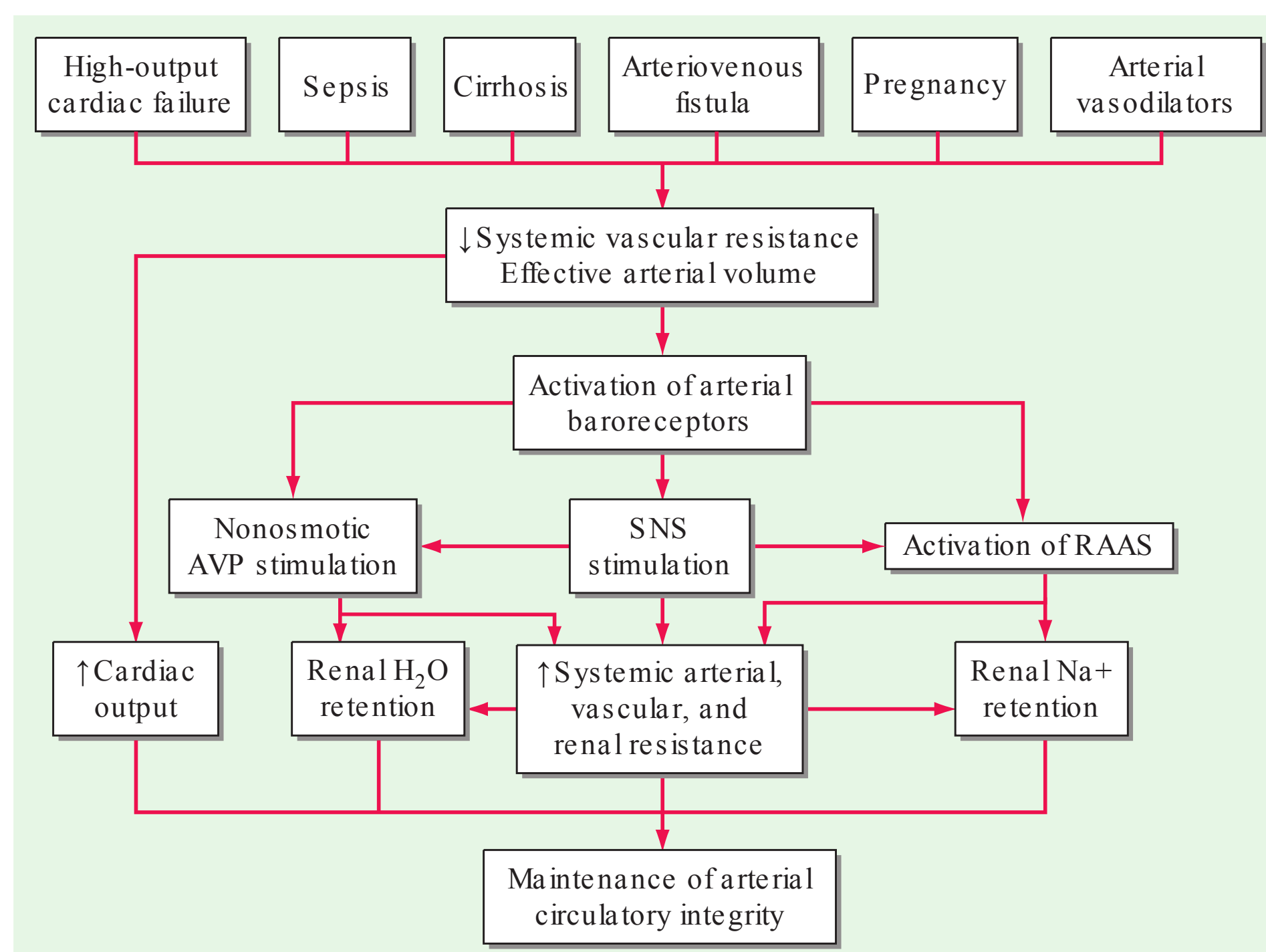
Edema may also result from damage to the capillary endothelium, which increases its permeability and permits the transfer of proteins into the interstitial compartment. Injury to the capillary wall can result from drugs (see below), viral or bacterial agents, and thermal or mechanical trauma. Increased capillary permeability also may be a consequence of a hypersensitivity reaction and of immune injury. Damage to the capillary endothelium is presumably responsible for inflammatory edema, which is usually nonpitting, localized, and accompanied by other signs of inflammation—i.e., erythema, heat, and tenderness.

REDUCTION OF EFFECTIVE ARTERIAL VOLUME

In many forms of edema, despite the increase in extracellular fluid volume, the effective arterial blood volume, a parameter that represents the filling of the arterial tree and that effectively perfuses the tissues, is reduced. Underfilling of the arterial tree may be caused by a reduction of cardiac output and/or systemic vascular resistance, by pooling of blood in the splanchnic veins (as in cirrhosis), and by hypoalbuminemia (**Fig. 7-1A**). As a consequence of underfilling, a series of physiologic responses designed to restore the effective arterial volume to normal are set into motion. A key element of these responses is the renal retention of



A



B

FIGURE 7-1

Clinical conditions in which a decrease in cardiac output (A) and systemic vascular resistance (B) cause arterial underfilling with resulting neurohumoral activation and renal sodium and water retention. In addition to activating the neurohumoral axis, adrenergic stimulation causes renal vasoconstriction and

enhances sodium and fluid transport by the proximal tubule epithelium. RAAS, renin-angiotensin aldosterone system; SNS, sympathetic nervous system. (Modified from RW Schrier: *Ann Intern Med* 113:155, 1990.)

sodium and, therefore, water, thereby restoring effective arterial volume, but sometimes also leading to or intensifying edema.

RENAL FACTORS AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The diminished renal blood flow characteristic of states in which the effective arterial blood volume is reduced is translated by the renal juxtaglomerular cells (specialized myoepithelial cells surrounding the afferent arteriole) into a signal for increased renin release. Renin is an enzyme with a molecular mass of about 40,000 Da that acts on its substrate, angiotensinogen, an α_2 -globulin synthesized by the liver, to release angiotensin I, a decapeptide, which in turn is converted to angiotensin II (AII), an octapeptide. AII has generalized vasoconstrictor properties, particularly on the renal efferent arterioles. Its action reduces the hydrostatic pressure in the peritubular capillaries, whereas the increased filtration fraction raises the colloid osmotic pressure in these vessels, thereby enhancing salt and water reabsorption in the proximal tubule as well as in the ascending limb of the loop of Henle.

The renin-angiotensin-aldosterone system (RAAS) operates as both a hormonal and paracrine system. Its activation causes sodium and water retention and thereby contributes to edema formation. Blockade of the conversion of angiotensin I to AII and blockade of the AII receptor enhance sodium and water excretion and reduce many forms of edema. AII that enters the systemic circulation stimulates the production of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone in turn enhances sodium reabsorption (and potassium excretion) by the collecting tubule, further favoring edema formation. In patients with heart failure, not only is aldosterone secretion elevated but the biologic half-life of the hormone is prolonged secondary to the depression of hepatic blood flow, which reduces its hepatic catabolism and increases further the plasma level of the hormone. Blockade of the action of aldosterone by spironolactone or eplerenone (aldosterone antagonists) or by amiloride (a blocker of epithelial sodium channels) often induces a moderate diuresis in edematous states.

ARGININE VASOPRESSIN

The secretion of arginine vasopressin (AVP) occurs in response to increased intracellular osmolar concentration, and, by stimulating V_2 receptors, AVP increases the reabsorption of free water in the distal tubules and collecting ducts of the kidneys, thereby increasing total-body water. Circulating AVP is elevated in many patients with heart failure secondary to a nonosmotic stimulus associated with decreased effective arterial

volume and reduced compliance of the left atrium. Such patients fail to show the normal reduction of AVP with a reduction of osmolality, contributing to edema formation and hyponatremia.

ENDOTHELIN-1

This potent peptide vasoconstrictor is released by endothelial cells. Its concentration in the plasma is elevated in patients with severe heart failure and contributes to renal vasoconstriction, sodium retention, and edema.

NATRIURETIC PEPTIDES

Atrial distention causes release into the circulation of atrial natriuretic peptide (ANP), a polypeptide; a high-molecular-weight precursor of ANP is stored in secretory granules within atrial myocytes. The closely related brain natriuretic peptide (pre-prohormone BNP) is stored primarily in ventricular myocytes and is released when ventricular diastolic pressure rises. Released ANP and BNP (which is derived from its precursor) bind to the natriuretic receptor-A, which causes: (1) excretion of sodium and water by augmenting glomerular filtration rate, inhibiting sodium reabsorption in the proximal tubule, and inhibiting release of renin and aldosterone; and (2) dilation of arterioles and venules by antagonizing the vasoconstrictor actions of AII, AVP, and sympathetic stimulation. Thus, elevated levels of natriuretic peptides have the capacity to oppose sodium retention in hypervolemic and edematous states.

Although circulating levels of ANP and BNP are elevated in heart failure and in cirrhosis with ascites, the natriuretic peptides are not sufficiently potent to prevent edema formation. Indeed, in edematous states, resistance to the actions of natriuretic peptides may be increased, further reducing their effectiveness.

CLINICAL CAUSES OF EDEMA

A weight gain of several kilograms usually precedes overt manifestations of generalized edema, and a similar weight loss from diuresis can be induced in a slightly edematous patient before “dry weight” is achieved. Anasarca refers to gross, generalized edema. Ascites and hydrothorax refer to accumulation of excess fluid in the peritoneal and pleural cavities, respectively, and are considered special forms of edema.

Edema is recognized by the persistence of an indentation of the skin after pressure; this is known as “pitting” edema. In its more subtle form, edema may be detected by noting that after the stethoscope is removed from the chest wall, the rim of the bell leaves an indentation on the skin of the chest for a few minutes. Edema

60 may be present when the ring on a finger fits more snugly than in the past or when a patient complains of difficulty putting on shoes, particularly in the evening. Edema may also be recognized by puffiness of the face, which is most readily apparent in the periorbital areas.

GENERALIZED EDEMA

The differences among the major causes of generalized edema are shown in Table 7-1. Cardiac, renal, hepatic, or nutritional disorders are responsible for a majority of patients with generalized edema. Consequently, the differential diagnosis of generalized edema should be directed toward identifying or excluding these several conditions.

Heart failure

(See also Chap. 19) In heart failure, the impaired systolic emptying of the ventricle(s) and/or the impairment of ventricular relaxation promotes an accumulation of blood in the venous circulation at the

expense of the effective arterial volume. In addition, the heightened tone of the sympathetic nervous system causes renal vasoconstriction and reduction of glomerular filtration. In mild heart failure, a small increment of total blood volume may repair the deficit of effective arterial volume through the operation of Starling’s law of the heart, in which an increase in ventricular diastolic volume promotes a more forceful contraction and may thereby maintain the cardiac output. However, if the cardiac disorder is more severe, sodium and water retention continue, and the increment in blood volume accumulates in the venous circulation, raising venous pressure and causing edema (Fig. 7-1).

The presence of heart disease, as manifested by cardiac enlargement and/or ventricular hypertrophy, together with evidence of cardiac failure, such as dyspnea, basilar rales, venous distention, and hepatomegaly, usually indicates that edema results from heart failure. Noninvasive tests such as echocardiography may be helpful in establishing the diagnosis of heart disease. The edema of heart failure typically occurs in the dependent portions of the body.

TABLE 7-1

PRINCIPAL CAUSES OF GENERALIZED EDEMA: HISTORY, PHYSICAL EXAMINATION, AND LABORATORY FINDINGS			
ORGAN SYSTEM	HISTORY	PHYSICAL EXAMINATION	LABORATORY FINDINGS
Cardiac	Dyspnea with exertion prominent—often associated with orthopnea—or paroxysmal nocturnal dyspnea	Elevated jugular venous pressure, ventricular (S ₃) gallop; occasionally with displaced or dyskinetic apical pulse; peripheral cyanosis, cool extremities, small pulse pressure when severe	Elevated urea nitrogen-to-creatinine ratio common; serum sodium often diminished; elevated natriuretic peptides
Hepatic	Dyspnea uncommon, except if associated with significant degree of ascites; most often a history of ethanol abuse	Frequently associated with ascites; jugular venous pressure normal or low; blood pressure lower than in renal or cardiac disease; one or more additional signs of chronic liver disease (jaundice, palmar erythema, Dupuytren’s contracture, spider angiomas, male gynecomastia; asterix and other signs of encephalopathy) may be present	If severe, reductions in serum albumin, cholesterol, other hepatic proteins (transferrin, fibrinogen); liver enzymes elevated, depending on the cause and acuity of liver injury; tendency toward hypokalemia, respiratory alkalosis; macrocytosis from folate deficiency
Renal (CRF)	Usually chronic: may be associated with uremic signs and symptoms, including decreased appetite, altered (metallic or fishy) taste, altered sleep pattern, difficulty concentrating, restless legs, or myoclonus; dyspnea can be present, but generally less prominent than in heart failure	Elevated blood pressure; hypertensive retinopathy; nitrogenous fetor; pericardial friction rub in advanced cases with uremia	Elevation of serum creatinine and cystatin C; albuminuria; hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, anemia (usually normocytic)
Renal (NS)	Childhood diabetes mellitus; plasma cell dyscrasias	Periorbital edema; hypertension	Proteinuria (≥3.5 g/d); hypoalbuminemia; hypercholesterolemia; microscopic hematuria

Abbreviations: CRF, chronic renal failure; NS, nephrotic syndrome.
Source: Modified from GM Chertow: Approach to the patient with edema, in Primary Cardiology, 2nd ed, E Braunwald, L Goldman (eds). Philadelphia, Saunders, 2003, pp 117–128.

Edema of renal disease

(See also Chap. 15) The edema that occurs during the acute phase of glomerulonephritis is characteristically associated with hematuria, proteinuria, and hypertension. Although some evidence supports the view that the fluid retention is due to increased capillary permeability, in most instances, the edema results from primary retention of sodium and water by the kidneys owing to renal insufficiency. This state differs from most forms of heart failure in that it is characterized by a normal (or sometimes even increased) cardiac output. Patients with edema due to acute renal failure commonly have arterial hypertension as well as pulmonary congestion on chest roentgenogram, often without considerable cardiac enlargement, but they may not develop orthopnea. Patients with chronic renal failure may also develop edema due to primary renal retention of sodium and water.

Nephrotic syndrome and other hypoalbuminemic states

The primary alteration in the nephrotic syndrome is a diminished colloid oncotic pressure due to losses of large quantities (≥ 3.5 g/d) of protein into the urine. With severe hypoalbuminemia (< 35 g/L) and the consequent reduced colloid osmotic pressure, the sodium and water that are retained cannot be restrained within the vascular compartment, and total and effective arterial blood volumes decline. This process initiates the edema-forming sequence of events described above, including activation of the RAAS. The nephrotic syndrome may occur during the course of a variety of kidney diseases, which include glomerulonephritis, diabetic glomerulosclerosis, and hypersensitivity reactions. The edema is diffuse, symmetric, and most prominent in the dependent areas; as a consequence, periorbital edema is most prominent in the morning.

Hepatic cirrhosis

This condition is characterized in part by hepatic venous outflow blockade, which in turn expands the splanchnic blood volume and increases hepatic lymph formation. Intrahepatic hypertension acts as a stimulus for renal sodium retention and causes a reduction of effective arterial blood volume. These alterations are frequently complicated by hypoalbuminemia secondary to reduced hepatic synthesis of albumin, as well as peripheral arterial vasodilation. These effects reduce the effective arterial blood volume further, leading to activation of the RAAS and renal sympathetic nerves and to release of AVP, endothelin, and other sodium- and water-retaining mechanisms (Fig. 7-1B). The concentration of circulating aldosterone often is elevated by the failure of the liver to metabolize this hormone. Initially, the excess

interstitial fluid is localized preferentially proximal (upstream) to the congested portal venous system and obstructed hepatic lymphatics, i.e., in the peritoneal cavity (causing ascites). In later stages, particularly when there is severe hypoalbuminemia, peripheral edema may develop. A sizable accumulation of ascitic fluid may increase intraabdominal pressure and impede venous return from the lower extremities and contribute to the accumulation of edema of the lower extremities.

The excess production of prostaglandins (PGE_2 and PGI_2) in cirrhosis attenuates renal sodium retention. When the synthesis of these substances is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs), renal function may deteriorate, and this may increase sodium retention further.

Drug-induced edema

A large number of widely used drugs can cause edema (Table 7-2). Mechanisms include renal vasoconstriction (NSAIDs and cyclosporine), arteriolar dilation

TABLE 7-2

DRUGS ASSOCIATED WITH EDEMA FORMATION

Nonsteroidal anti-inflammatory drugs

Antihypertensive agents

Direct arterial/arteriolar vasodilators

Hydralazine

Clonidine

Methyldopa

Guanethidine

Minoxidil

Calcium channel antagonists

α -Adrenergic antagonists

Thiazolidinediones

Steroid hormones

Glucocorticoids

Anabolic steroids

Estrogens

Progestins

Cyclosporine

Growth hormone

Immunotherapies

Interleukin 2

OKT3 monoclonal antibody

Source: Modified from Chertow GM: Approach to the patient with edema, in Primary Cardiology, 2nd ed, E Braunwald, L Goldman (eds). Philadelphia, Saunders, 2003, pp 117–128.

62 (vasodilators), augmented renal sodium reabsorption (steroid hormones), and capillary damage.

Edema of nutritional origin

A diet grossly deficient in protein over a prolonged period may produce hypoproteinemia and edema. The latter may be intensified by the development of beriberi heart disease, which also is of nutritional origin, in which multiple peripheral arteriovenous fistulae result in reduced effective systemic perfusion and effective arterial blood volume, thereby enhancing edema formation (**Fig. 7-1B**). Edema may actually become intensified when famished subjects are first provided with an adequate diet. The ingestion of more food may increase the quantity of sodium ingested, which is then retained along with water. So-called refeeding edema also may be linked to increased release of insulin, which directly increases tubular sodium reabsorption. In addition to hypoalbuminemia, hypokalemia and caloric deficits may be involved in the edema of starvation.

LOCALIZED EDEMA

In this condition, the hydrostatic pressure in the capillary bed upstream (proximal) of the obstruction increases so that an abnormal quantity of fluid is transferred from the vascular to the interstitial space. Since the alternative route (i.e., the lymphatic channels) also may be obstructed or maximally filled, an increased volume of interstitial fluid in the limb develops (i.e., there is trapping of fluid in the interstitium of the extremity). The displacement of large quantities of fluid into a limb may occur at the expense of the blood volume in the remainder of the body, thereby reducing effective arterial blood volume and leading to the retention of NaCl and H₂O until the deficit in plasma volume has been corrected.

Localized edema due to venous or lymphatic obstruction may be caused by thrombophlebitis, chronic lymphangitis, resection of regional lymph nodes, and filariasis, among other causes. Lymphedema is particularly intractable because restriction of lymphatic flow results in increased protein concentration in the interstitial fluid, a circumstance that aggravates fluid retention.

Other causes of edema

These causes include hypothyroidism (myxedema) and hyperthyroidism (pretibial myxedema secondary to Graves' disease), the edema in which is typically non-pitting and due to deposition of hyaluronic acid and, in

Graves' disease, lymphocytic infiltration and inflammation; exogenous hyperadrenocortism; pregnancy; and administration of estrogens and vasodilators, particularly dihydropyridines such as nifedipine.

DISTRIBUTION OF EDEMA

The distribution of edema is an important guide to its cause. Edema associated with heart failure tends to be more extensive in the legs and to be accentuated in the evening, a feature also determined largely by posture. When patients with heart failure are confined to bed, edema may be most prominent in the presacral region. Severe heart failure may cause ascites that may be distinguished from the ascites caused by hepatic cirrhosis by the jugular venous pressure, which is usually elevated in heart failure and normal in cirrhosis.

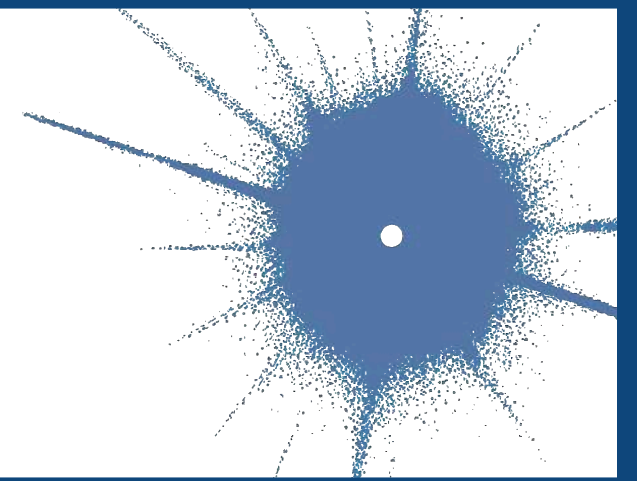
Edema resulting from hypoproteinemia, as occurs in the nephrotic syndrome, characteristically is generalized, but it is especially evident in the very soft tissues of the eyelids and face and tends to be most pronounced in the morning owing to the recumbent posture assumed during the night. Less common causes of facial edema include trichinosis, allergic reactions, and myxedema. Edema limited to one leg or to one or both arms is usually the result of venous and/or lymphatic obstruction. Unilateral paralysis reduces lymphatic and venous drainage on the affected side and may also be responsible for unilateral edema. In patients with obstruction of the superior vena cava, edema is confined to the face, neck, and upper extremities in which the venous pressure is elevated compared with that in the lower extremities.

APPROACH TO THE PATIENT: Edema

An important first question is whether the edema is localized or generalized. If it is localized, the local phenomena that may be responsible should be considered. If the edema is generalized, one should first determine if there is serious hypoalbuminemia, e.g., serum albumin <25 g/L. If so, the history, physical examination, urinalysis, and other laboratory data will help evaluate the question of cirrhosis, severe malnutrition, or the nephrotic syndrome as the underlying disorder. If hypoalbuminemia is not present, it should be determined if there is evidence of heart failure severe enough to promote generalized edema. Finally, it should be ascertained as to whether or not the patient has an adequate urine output or if there is significant oliguria or anuria.

CHAPTER 8

PALPITATIONS



Joseph Loscalzo

Palpitations are extremely common among patients who present to their internists and can best be defined as an intermittent “thumping,” “pounding,” or “fluttering” sensation in the chest. This sensation can be either intermittent or sustained and either regular or irregular. Most patients interpret palpitations as an unusual awareness of the heartbeat and become especially concerned when they sense that they have had “skipped” or “missing” heartbeats. Palpitations are often noted when the patient is quietly resting, during which time other stimuli are minimal. Palpitations that are positional generally reflect a structural process within (e.g., atrial myxoma) or adjacent to (e.g., mediastinal mass) the heart.

Palpitations are brought about by cardiac (43%), psychiatric (31%), miscellaneous (10%), and unknown (16%) causes, according to one large series. Among the cardiovascular causes are premature atrial and ventricular contractions, supraventricular and ventricular arrhythmias, mitral valve prolapse (with or without associated arrhythmias), aortic insufficiency, atrial myxoma, and pulmonary embolism. Intermittent palpitations are commonly caused by premature atrial or ventricular contractions: the post-extrasystolic beat is sensed by the patient owing to the increase in ventricular end-diastolic dimension following the pause in the cardiac cycle and the increased strength of contraction (post-extrasystolic potentiation) of that beat. Regular, sustained palpitations can be caused by regular supraventricular and ventricular tachycardias. Irregular, sustained palpitations can be caused by atrial fibrillation. It is important to note that most arrhythmias are not associated with palpitations. In those that are, it is often useful either to ask the patient to “tap out” the rhythm of the palpitations or to take his/her pulse during palpitations. In general, hyperdynamic cardiovascular states caused by catecholaminergic stimulation from exercise, stress, or pheochromocytoma can lead to palpitations. Palpitations are common among

athletes, especially older endurance athletes. In addition, the enlarged ventricle of aortic regurgitation and accompanying hyperdynamic precordium frequently lead to the sensation of palpitations. Other factors that enhance the strength of myocardial contraction, including tobacco, caffeine, aminophylline, atropine, thyroxine, cocaine, and amphetamines, can cause palpitations.

Psychiatric causes of palpitations include panic attacks or disorders, anxiety states, and somatization, alone or in combination. Patients with psychiatric causes for palpitations more commonly report a longer duration of the sensation (>15 min) and other accompanying symptoms than do patients with other causes. Among the miscellaneous causes of palpitations are thyrotoxicosis, drugs (see above) and ethanol, spontaneous skeletal muscle contractions of the chest wall, pheochromocytoma, and systemic mastocytosis.

APPROACH TO THE PATIENT

Palpitations

The principal goal in assessing patients with palpitations is to determine whether the symptom is caused by a life-threatening arrhythmia. Patients with preexisting coronary artery disease (CAD) or risk factors for CAD are at greatest risk for ventricular arrhythmias (**Chap. 17**) as a cause for palpitations. In addition, the association of palpitations with other symptoms suggesting hemodynamic compromise, including syncope or lightheadedness, supports this diagnosis. Palpitations caused by sustained tachyarrhythmias in patients with CAD can be accompanied by angina pectoris or dyspnea, and, in patients with ventricular dysfunction (systolic or diastolic), aortic stenosis, hypertrophic cardiomyopathy, or mitral stenosis (with or without CAD), can be accompanied by dyspnea from increased left atrial and pulmonary venous pressure.

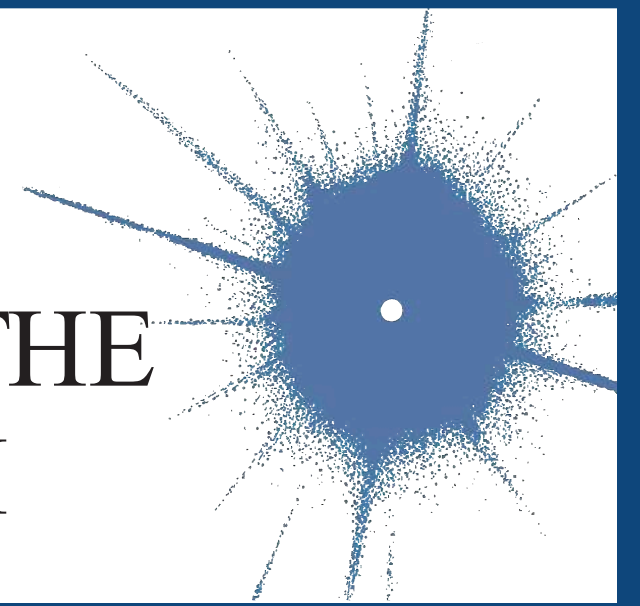
Key features of the physical examination that will help confirm or refute the presence of an arrhythmia as a cause for palpitations (as well as its adverse hemodynamic consequences) include measurement of the vital signs, assessment of the jugular venous pressure and pulse, and auscultation of the chest and precordium. A resting electrocardiogram can be used to document the arrhythmia. If exertion is known to induce the arrhythmia and accompanying palpitations, exercise electrocardiography can be used to make the diagnosis. If the arrhythmia is sufficiently infrequent, other methods must be used, including continuous electrocardiographic (Holter) monitoring; telephonic monitoring, through which the patient can transmit an electrocardiographic tracing during a sensed episode; loop recordings (external or implantable), which can capture the electrocardiographic event for later review; and mobile cardiac outpatient telemetry. Data suggest that Holter monitoring is of limited clinical utility, while the implantable loop recorder and mobile cardiac

outpatient telemetry are safe and possibly more cost-effective in the assessment of patients with (infrequent) recurrent, unexplained palpitations.

Most patients with palpitations do not have serious arrhythmias or underlying structural heart disease. If sufficiently troubling to the patient, occasional benign atrial or ventricular premature contractions can often be managed with beta-blocker therapy. Palpitations incited by alcohol, tobacco, or illicit drugs need to be managed by abstinence, while those caused by pharmacologic agents should be addressed by considering alternative therapies when appropriate or possible. Psychiatric causes of palpitations may benefit from cognitive therapy or pharmacotherapy. The physician should note that palpitations are at the very least bothersome and, on occasion, frightening to the patient. Once serious causes for the symptom have been excluded, the patient should be reassured that the palpitations will not adversely affect prognosis.

CHAPTER 9

PHYSICAL EXAMINATION OF THE CARDIOVASCULAR SYSTEM



Patrick T. O’Gara ■ Joseph Loscalzo

The approach to a patient with known or suspected cardiovascular disease begins with the time-honored traditions of a directed history and a targeted physical examination. The scope of these activities depends on the clinical context at the time of presentation, ranging from an elective ambulatory follow-up visit to a more focused emergency department encounter. There has been a gradual decline in physical examination skills over the last two decades at every level, from student to faculty specialist, a development of great concern to both clinicians and medical educators. Classic cardiac findings are recognized by only a minority of internal medicine and family practice residents. Despite popular perceptions, clinical performance does not improve predictably as a function of experience; instead, the acquisition of new examination skills may become more difficult for a busy individual practitioner. Less time is now devoted to mentored cardiovascular examinations during the training of students and residents. One widely recognized outcome of these trends is the progressive overutilization of noninvasive imaging studies to establish the presence and severity of cardiovascular disease even when the examination findings imply a low pretest probability of significant pathology. Educational techniques to improve bedside skills include repetition, patient-centered teaching conferences, and visual display feedback of auscultatory events with Doppler echocardiographic imaging.

The evidence base that links the findings from the history and physical examination to the presence, severity, and prognosis of cardiovascular disease has been established most rigorously for coronary artery disease, heart failure, and valvular heart disease. For example, observations regarding heart rate, blood pressure, signs of pulmonary congestion, and the presence of mitral

regurgitation (MR) contribute importantly to bedside risk assessment in patients with acute coronary syndromes. Observations from the physical examination in this setting can inform clinical decision making before the results of cardiac biomarkers testing are known. The prognosis of patients with systolic heart failure can be predicted on the basis of the jugular venous pressure (JVP) and the presence or absence of a third heart sound (S_3). Accurate characterization of cardiac murmurs provides important insight into the natural history of many valvular and congenital heart lesions. Finally, the important role played by the physical examination in enhancing the clinician-patient relationship cannot be overestimated.

THE GENERAL PHYSICAL EXAMINATION

Any examination begins with an assessment of the general appearance of the patient, with notation of age, posture, demeanor, and overall health status. Is the patient in pain or resting quietly, dyspneic or diaphoretic? Does the patient choose to avoid certain body positions to reduce or eliminate pain, as might be the case with suspected acute pericarditis? Are there clues indicating that dyspnea may have a pulmonary cause, such as a barrel chest deformity with an increased anterior-posterior diameter, tachypnea, and pursed-lip breathing? Skin pallor, cyanosis, and jaundice can be appreciated readily and provide additional clues. A chronically ill-appearing emaciated patient may suggest the presence of long-standing heart failure or another systemic disorder, such as a malignancy. Various genetic syndromes, often with cardiovascular involvement, can also be recognized easily, such as trisomy 21, Marfan’s syndrome, and Holt-Oram syndrome. Height and weight should be measured routinely, and both body

mass index and body surface area should be calculated. Knowledge of the waist circumference and the waist-to-hip ratio can be used to predict long-term cardiovascular risk. Mental status, level of alertness, and mood should be assessed continuously during the interview and examination.

Skin

Central cyanosis occurs with significant right-to-left shunting at the level of the heart or lungs, allowing deoxygenated blood to reach the systemic circulation. Peripheral cyanosis or acrocyanosis, in contrast, is usually related to reduced extremity blood flow due to small vessel constriction, as seen in patients with severe heart failure, shock, or peripheral vascular disease; it can be aggravated by the use of β -adrenergic blockers with unopposed α -mediated constriction. Differential cyanosis refers to isolated cyanosis affecting the lower but not the upper extremities in a patient with a large patent ductus arteriosus (PDA) and secondary pulmonary hypertension with right-to-left to shunting at the great vessel level. Hereditary telangiectasias on the lips, tongue, and mucous membranes, as part of the Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia), resemble spider nevi and can be a source of right-to-left shunting when also present in the lung. Malar telangiectasias also are seen in patients with advanced mitral stenosis and scleroderma. An unusually tan or bronze discoloration of the skin may suggest hemochromatosis as the cause of the associated systolic heart failure. Jaundice, which may be visible first in the sclerae, has a broad differential diagnosis but, in the appropriate setting, can be consistent with advanced right heart failure and congestive hepatomegaly or late-term “cardiac cirrhosis.” Cutaneous ecchymoses are seen frequently among patients taking vitamin K antagonists or antiplatelet agents such as aspirin and thienopyridines. Various lipid disorders sometimes are associated with subcutaneous xanthomas, particularly along the tendon sheaths or over the extensor surfaces of the extremities. Severe hypertriglyceridemia can be associated with eruptive xanthomatosis and lipemia retinalis. Palmar crease xanthomas are specific for type III hyperlipoproteinemia. Pseudoxanthoma elasticum, a disease associated with premature atherosclerosis, is manifested by a leathery, cobblestoned appearance of the skin in the axilla and neck creases and by angioid streaks on funduscopic examination. Extensive lentiginoses have been described in a variety of development delay–cardiovascular syndromes, including Carney’s syndrome, which includes multiple atrial myxomas. Cutaneous manifestations of sarcoidosis such as lupus pernio and erythema nodosum may suggest this disease as a cause of an associated dilated cardiomyopathy,

especially with heart block, intraventricular conduction delay, or ventricular tachycardia.

Head and neck

Dentition and oral hygiene should be assessed in every patient both as a source of potential infection and as an index of general health. A high-arched palate is a feature of Marfan’s syndrome and other connective tissue disease syndromes. Bifid uvula has been described in patients with Loeys-Dietz syndrome, and orange tonsils are characteristic of Tangier disease. The ocular manifestations of hyperthyroidism have been well described. Many patients with congenital heart disease have associated hypertelorism, low-set ears, or micrognathia. Blue sclerae are a feature of osteogenesis imperfecta. An arcus senilis pattern lacks specificity as an index of coronary heart disease risk. The funduscopic examination is an often underused method by which to assess the microvasculature, especially among patients with established atherosclerosis, hypertension, or diabetes mellitus. A mydriatic agent may be necessary for optimal visualization. A funduscopic examination should be performed routinely in the assessment of patients with suspected endocarditis and those with a history of acute visual change. Branch retinal artery occlusion or visualization of a Hollenhorst plaque can narrow the differential diagnosis rapidly in the appropriate setting. Relapsing polychondritis may manifest as an inflamed pinna or, in its later stages, as a saddle-nose deformity because of destruction of nasal cartilage; granulomatosis with polyangiitis (Wegener’s) can also lead to a saddle-nose deformity.

Chest

Midline sternotomy, left posterolateral thoracotomy, or infraclavicular scars at the site of pacemaker/defibrillator generator implantation should not be overlooked and may provide the first clue regarding an underlying cardiovascular disorder in patients unable to provide a relevant history. A prominent venous collateral pattern may suggest subclavian or vena caval obstruction. If the head and neck appear dusky and slightly cyanotic and the venous pressure is grossly elevated without visible pulsations, a diagnosis of superior vena cava syndrome should be entertained. Thoracic cage abnormalities have been well described among patients with connective tissue disease syndromes. They include pectus carinatum (“pigeon chest”) and pectus excavatum (“funnel chest”). Obstructive lung disease is suggested by a barrel chest deformity, especially with tachypnea, pursed-lip breathing, and use of accessory muscles. The characteristically severe kyphosis and compensatory lumbar, pelvic, and knee flexion of

ankylosing spondylitis should prompt careful auscultation for a murmur of aortic regurgitation (AR). Straight back syndrome refers to the loss of the normal kyphosis of the thoracic spine and has been described in patients with mitral valve prolapse (MVP) and its variants. In some patients with cyanotic congenital heart disease, the chest wall appears to be asymmetric, with anterior displacement of the left hemithorax. The respiratory rate and pattern should be noted during spontaneous breathing, with additional attention to depth, audible wheezing, and stridor. Lung examination can reveal adventitious sounds indicative of pulmonary edema, pneumonia, or pleuritis.

Abdomen

In some patients with advanced obstructive lung disease, the point of maximal cardiac impulse may be in the epigastrium. The liver is frequently enlarged and tender in patients with chronic heart failure. Systolic pulsations over the liver signify severe tricuspid regurgitation (TR). Splenomegaly may be a feature of infective endocarditis, particularly when symptoms have persisted for weeks or months. Ascites is a nonspecific finding but may be present with advanced chronic right heart failure, constrictive pericarditis, hepatic cirrhosis, or an intraperitoneal malignancy. The finding of an elevated JVP implies a cardiovascular etiology. In nonobese patients, the aorta typically is palpated between the epigastrium and the umbilicus. The sensitivity of palpation for the detection of an abdominal aortic aneurysm (pulsatile and expansile mass) decreases as a function of body size. Because palpation alone is not sufficiently accurate to establish this diagnosis, a screening ultrasound examination is advised. The presence of an arterial bruit over the abdomen suggests high-grade atherosclerotic disease, although precise localization is difficult.

Extremities

The temperature and color of the extremities, the presence of clubbing, arachnodactyly, and pertinent nail findings can be surmised quickly during the examination. Clubbing implies the presence of central right-to-left shunting, although it has also been described in patients with endocarditis. Its appearance can range from cyanosis and softening of the root of the nail bed, to the classic loss of the normal angle between the base of the nail and the skin, to the skeletal and periosteal bony changes of hypertrophic osteoarthropathy, which is seen rarely in patients with advanced lung or liver disease. Patients with the Holt-Oram syndrome have an unopposable, “fingerized” thumb, whereas patients with Marfan’s syndrome may have arachnodactyly and a positive “wrist” (overlapping of the thumb

and fifth finger around the wrist) or “thumb” (protrusion of the thumb beyond the ulnar aspect of the hand when the fingers are clenched over the thumb in a fist) sign. The Janeway lesions of endocarditis are nontender, slightly raised hemorrhages on the palms and soles, whereas Osler’s nodes are tender, raised nodules on the pads of the fingers or toes. Splinter hemorrhages are classically identified as linear petechiae in the midposition of the nail bed and should be distinguished from the more common traumatic petechiae, which are seen closer to the distal edge.

Lower extremity or presacral edema in the setting of an elevated JVP defines volume overload and may be a feature of chronic heart failure or constrictive pericarditis. Lower extremity edema in the absence of jugular venous hypertension may be due to lymphatic or venous obstruction or, more commonly, to venous insufficiency, as further suggested by the appearance of varicosities, venous ulcers (typically medial in location), and brownish cutaneous discoloration from hemosiderin deposition (eburnation). Pitting edema can also be seen in patients who use dihydropyridine calcium channel blockers. A Homan’s sign (posterior calf pain on active dorsiflexion of the foot against resistance) is neither specific nor sensitive for deep venous thrombosis. Muscular atrophy or the absence of hair along an extremity is consistent with severe arterial insufficiency or a primary neuromuscular disorder.

CARDIOVASCULAR EXAMINATION

Jugular venous pressure and waveform

JVP is the single most important bedside measurement from which to estimate the volume status. The internal jugular vein is preferred because the external jugular vein is valved and not directly in line with the superior vena cava and right atrium. Nevertheless, the external jugular vein has been used to discriminate between high and low central venous pressure (CVP) when tested among medical students, residents, and attending physicians. Precise estimation of the central venous or right atrial pressure from bedside assessment of the jugular venous waveform has proved difficult. Venous pressure traditionally has been measured as the vertical distance between the top of the jugular venous pulsation and the sternal inflection point (angle of Louis). A distance >4.5 cm at 30° elevation is considered abnormal. However, the actual distance between the mid-right atrium and the angle of Louis varies considerably as a function of both body size and the patient angle at which the assessment is made (30° , 45° , or 60°). The use of the sternal angle as a reference point leads to systematic underestimation of CVP, and this method should be used less for semiquantification

than to distinguish a normal from an abnormally elevated CVP. The use of the clavicle may provide an easier reference for standardization. Venous pulsations above this level in the sitting position are clearly abnormal, as the distance between the clavicle and the right atrium is at least 10 cm. The patient should always be placed in the sitting position, with the legs dangling below the bedside, when an elevated pressure is suspected in the semisupine position. It should also be noted that bedside estimates of CVP are made in centimeters of water but must be converted to millimeters of mercury to provide correlation with accepted hemodynamic norms ($1.36 \text{ cmH}_2\text{O} = 1.0 \text{ mmHg}$).

The venous waveform sometimes can be difficult to distinguish from the carotid pulse, especially during casual inspection. Nevertheless, the venous waveform has several characteristic features, and its individual components can be appreciated in most patients (Fig. 9-1). The arterial pulsation is not easily obliterated with palpation; the venous waveform in patients with sinus rhythm is usually biphasic, while the carotid pulse is monophasic; and the jugular venous pulsation should change with changes in posture or inspiration (unless the venous pressure is quite elevated).

The venous waveform is divided into several distinct peaks. The a wave reflects right atrial presystolic contraction and occurs just after the electrocardiographic P wave, preceding the first heart sound (S_1). A prominent a wave is seen in patients with reduced right ventricular compliance; a cannon a wave occurs with atrioventricular (AV) dissociation and right atrial contraction against a closed tricuspid valve. In a patient with a wide complex tachycardia, the appreciation of cannon a waves in the jugular venous waveform identifies the rhythm as ventricular in origin. The a wave is not present with atrial fibrillation. The x descent defines the fall in right atrial pressure after inscription of the a wave. The c wave interrupts this x descent and is followed by a further descent. The v wave represents atrial filling (atrial diastole) and occurs during ventricular systole. The height of the v wave is determined by right atrial compliance as well as the volume of blood returning to the right atrium either antegrade from the cavae or retrograde through an incompetent tricuspid valve. In patients with TR, the v wave is accentuated and the subsequent fall in pressure (y descent) is rapid. With progressive degrees of TR, the v wave merges with the c wave, and the right atrial and jugular vein waveforms become “ventricularized.” The y descent, which follows the peak of the v wave, can become prolonged or blunted with obstruction to right ventricular inflow, as may occur with tricuspid stenosis or pericardial tamponade. Normally, the venous pressure should fall by at least 3 mmHg with inspiration. Kussmaul’s sign is defined by either a rise or a lack of fall of the JVP with inspiration and is classically associated with constrictive

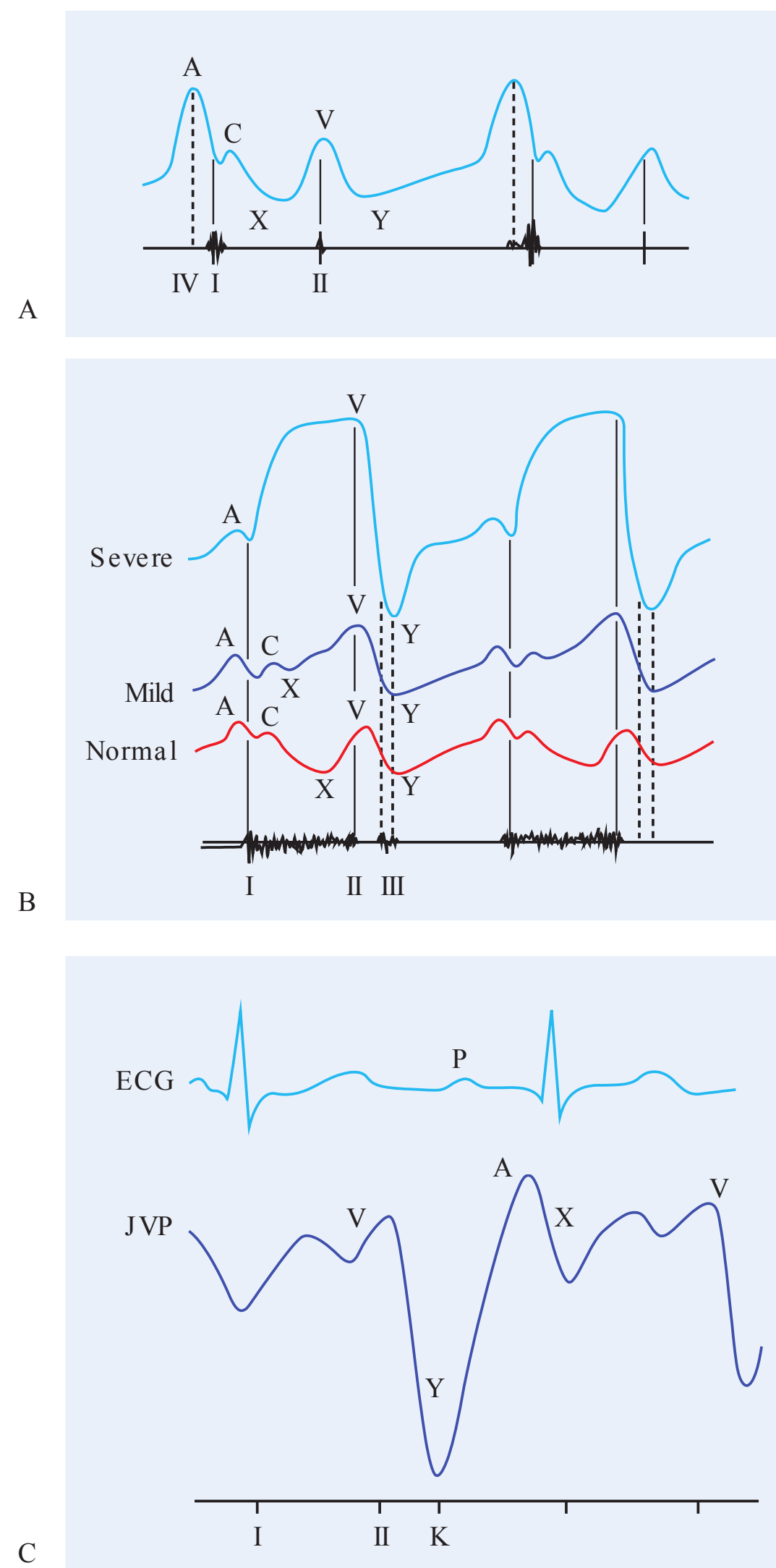


FIGURE 9-1

A. Jugular venous pulse wave tracing (top) with heart sounds (bottom). The A wave represents right atrial presystolic contraction and occurs just after the electrocardiographic P wave and just before the first heart sound (I). In this example, the A wave is accentuated and larger than normal due to decreased right ventricular compliance, as also suggested by the right-sided S_4 (IV). The C wave may reflect the carotid pulsation in the neck and/or an early systolic increase in right atrial pressure as the right ventricle pushes the closed tricuspid valve into the right atrium. The x descent follows the A wave just as atrial pressure continues to fall. The V wave represents atrial filling during ventricular systole and peaks at the second heart sound (II). The y descent corresponds to the fall in right atrial pressure after tricuspid valve opening. B. Jugular venous wave forms in mild (middle) and severe (top) tricuspid regurgitation, compared with normal, with phonocardiographic representation of the corresponding heart sounds below. With increasing degrees of tricuspid regurgitation, the waveform becomes “ventricularized.” C. Electrocardiogram (ECG) (top), jugular venous waveform (JVP) (middle), and heart sounds (bottom) in pericardial constriction. Note the prominent and rapid y descent, corresponding in timing to the pericardial knock (K). (From J Abrams: *Synopsis of Cardiac Physical Diagnosis*, 2nd ed. Boston, Butterworth Heinemann, 2001, pp 25–35.)

pericarditis, although it has been reported in patients with restrictive cardiomyopathy, massive pulmonary embolism, right ventricular infarction, and advanced left ventricular systolic heart failure. It is also a common, isolated finding in patients after cardiac surgery without other hemodynamic abnormalities.

Venous hypertension sometimes can be elicited by performance of the abdominojugular reflex or with passive leg elevation. When these signs are positive, a volume-overloaded state with limited compliance of an overly distended or constricted venous system is present. The abdominojugular reflex is elicited with firm and consistent pressure over the upper portion of the abdomen, preferably over the right upper quadrant, for at least 10 s. A positive response is defined by a sustained rise of more than 3 cm in the JVP during the application of firm abdominal pressure. The response should be assessed after 10 seconds of continuous pressure to allow for respiratory artifacts and tensing of the abdominal muscles to subside. Patients must be coached to refrain from breath holding or a Valsalva-like maneuver during the procedure. The abdominojugular reflex is useful in predicting a pulmonary artery wedge pressure in excess of 15 mmHg in patients with heart failure.

Although the JVP estimates right ventricular filling pressure, it has a predictable relationship with the pulmonary artery wedge pressure. In a large study of patients with advanced heart failure, the presence of a right atrial pressure >10 mmHg (as predicted on bedside examination) had a positive value of 88% for the prediction of a pulmonary artery wedge pressure of >22 mmHg. In addition, an elevated JVP has prognostic significance in patients with both symptomatic heart failure and asymptomatic left ventricular systolic dysfunction. The presence of an elevated JVP is associated with a higher risk of subsequent hospitalization for heart failure, death from heart failure, or both.

Assessment of blood pressure

Measurement of blood pressure usually is delegated to a medical assistant but should be repeated by the clinician. Accurate measurement depends on body position, arm size, time of measurement, place of measurement, device, device size, technique, and examiner. In general, physician-recorded blood pressures are higher than both nurse-recorded pressures and self-recorded pressures at home. Blood pressure is best measured in the seated position with the arm at the level of the heart, using an appropriately sized cuff, after 5–10 min of relaxation. When it is measured in the supine position, the arm should be raised to bring it to the level of the mid-right atrium. The length and width of the blood pressure cuff bladder should be 80% and 40% of the arm's circumference, respectively. A common

source of error in practice is to use an inappropriately small cuff, resulting in marked overestimation of true blood pressure, or an inappropriately large cuff, resulting in underestimation of true blood pressure. The cuff should be inflated to 30 mmHg above the expected systolic pressure and the pressure released at a rate of 2–3 mmHg/s. Systolic and diastolic pressures are defined by the first and fifth Korotkoff sounds, respectively. Very low (even 0 mmHg) diastolic blood pressures may be recorded in patients with chronic, severe AR or a large arteriovenous fistula because of enhanced diastolic “run-off.” In these instances, both the phase IV and phase V Korotkoff sounds should be recorded. Blood pressure is best assessed at the brachial artery level, though it can be measured at the radial, popliteal, or pedal pulse level. In general, systolic pressure increases and diastolic pressure decreases when measured in more distal arteries. Blood pressure should be measured in both arms, and the difference should be less than 10 mmHg. A blood pressure differential that exceeds this threshold may be associated with atherosclerotic or inflammatory subclavian artery disease, supraaortic stenosis, aortic coarctation, or aortic dissection. Systolic leg pressures are usually as much as 20 mmHg higher than systolic arm pressures. Greater leg–arm pressure differences are seen in patients with chronic severe AR as well as patients with extensive and calcified lower extremity peripheral arterial disease. The ankle-brachial index (lower pressure in the dorsalis pedis or posterior tibial artery divided by the higher of the two brachial artery pressures) is a powerful predictor of long-term cardiovascular mortality.

The blood pressure measured in an office or hospital setting may not accurately reflect the pressure in other venues. “White coat hypertension” is defined by at least three separate clinic-based measurements $>140/90$ mmHg and at least two non-clinic-based measurements $<140/90$ mmHg in the absence of any evidence of target organ damage. Individuals with white coat hypertension may not benefit from drug therapy, although they may be more likely to develop sustained hypertension over time. Masked hypertension should be suspected when normal or even low blood pressures are recorded in patients with advanced atherosclerotic disease, especially when evidence of target organ damage is present or bruits are audible.

Orthostatic hypotension is defined by a fall in systolic pressure >20 mmHg or in diastolic pressure >10 mmHg in response to assumption of the upright posture from a supine position within 3 min. There may also be a lack of a compensatory tachycardia, an abnormal response that suggests autonomic insufficiency, as may be seen in patients with diabetes or Parkinson's disease. Orthostatic hypotension is a common cause of postural lightheadedness/syncope and should be assessed routinely in patients for whom this diagnosis

might pertain. It can be exacerbated by advanced age, dehydration, certain medications, food, deconditioning, and ambient temperature.

Arterial pulse

The carotid artery pulse occurs just after the ascending aortic pulse. The aortic pulse is best appreciated in the epigastrium, just above the level of the umbilicus. Peripheral arterial pulses that should be assessed routinely include the subclavian, brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial. In patients in whom the diagnosis of either temporal arteritis or polymyalgia rheumatica is suspected, the temporal arteries also should be examined. Although one of the two pedal pulses may not be palpable in up to 10% of normal subjects, the pair should be symmetric. The integrity of the arcuate system of the hand is assessed by Allen's test, which is performed routinely before instrumentation of the radial artery. The pulses should be examined for their symmetry, volume, timing, contour, amplitude, and duration. If necessary, simultaneous auscultation of the heart can help identify a delay in the arrival of an arterial pulse. Simultaneous palpation of the radial and femoral pulses may reveal a femoral delay in a patient with hypertension and suspected aortic coarctation. The carotid upstrokes should never be examined simultaneously or before listening for a bruit. Light pressure should always be used to avoid precipitation of carotid hypersensitivity syndrome and syncope in a susceptible elderly individual. The arterial pulse usually becomes more rapid and spiking as a function of its distance from the heart, a phenomenon that reflects the muscular status of the more peripheral arteries and the summation of the incident and reflected waves. In general, the character and contour of the arterial pulse depend on the stroke volume, ejection velocity, vascular compliance, and systemic vascular resistance. The pulse examination can be misleading in patients with reduced cardiac output and in those with stiffened arteries from aging, chronic hypertension, or peripheral arterial disease.

The character of the pulse is best appreciated at the carotid level (**Fig. 9-2**). A weak and delayed pulse (pulsus parvus et tardus) defines severe aortic stenosis (AS). Some patients with AS may also have a slow, notched, or interrupted upstroke (anacrotic pulse) with a thrill or shudder. With chronic severe AR, by contrast, the carotid upstroke has a sharp rise and rapid fall-off (Corrigan's or water-hammer pulse). Some patients with advanced AR may have a bifid or bisferiens pulse, in which two systolic peaks can be appreciated. A bifid pulse is also described in patients with hypertrophic obstructive cardiomyopathy (HOCM), with inscription of percussion and tidal waves. A bifid pulse is easily

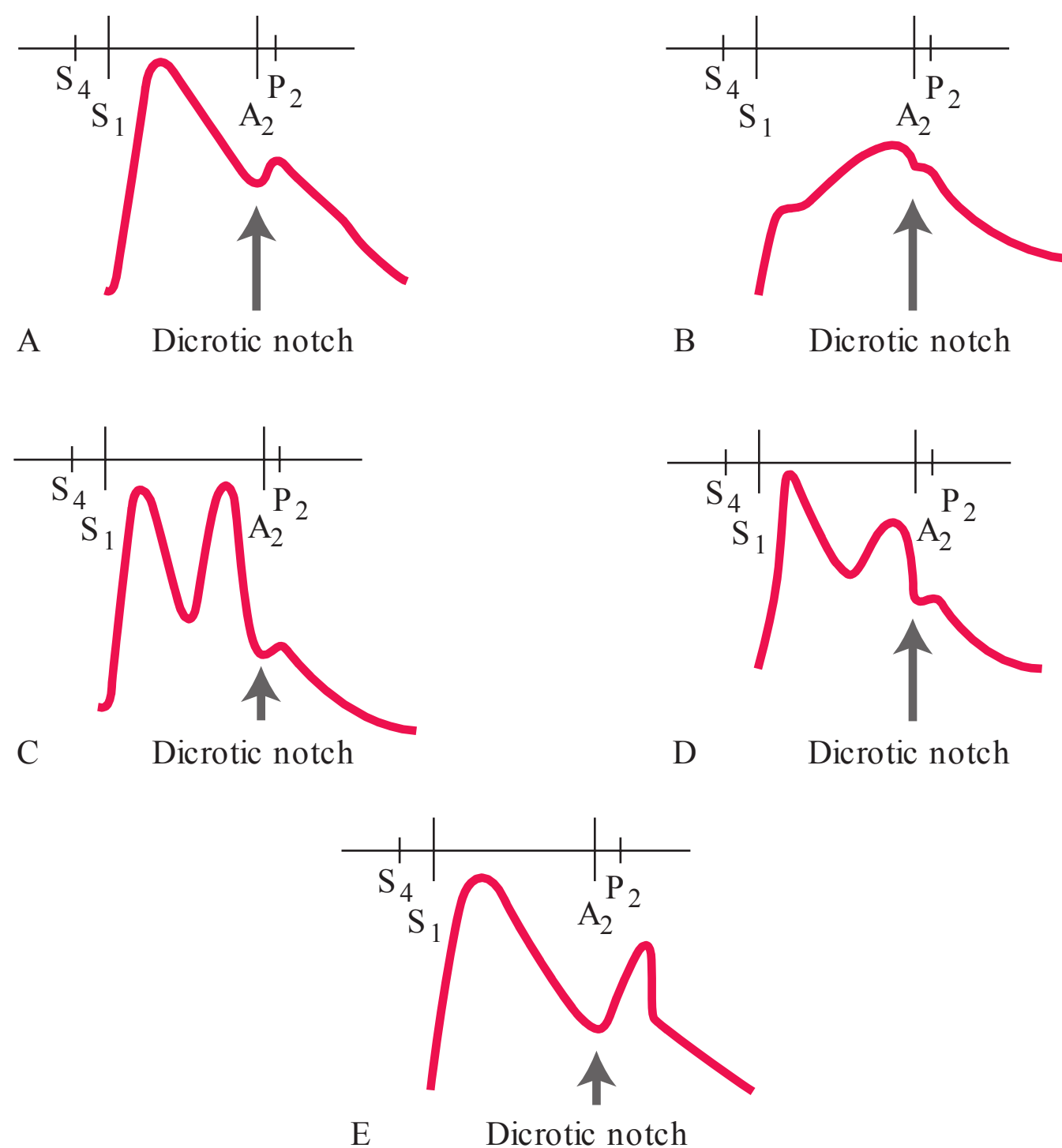


FIGURE 9-2

Schematic diagrams of the configurational changes in carotid pulse and their differential diagnoses. Heart sounds are also illustrated. A. Normal. S₄, fourth heart sound; S₁, first heart sound; A₂ aortic component of second heart sound; P₂ pulmonic component of second heart sound. B. Aortic stenosis. Anacrotic pulse with slow upstroke to a reduced peak. C. Bisferiens pulse with two peaks in systole. This pulse is rarely appreciated in patients with severe aortic regurgitation. D. Bisferiens pulse in hypertrophic obstructive cardiomyopathy. There is a rapid upstroke to the first peak (percussion wave) and a slower rise to the second peak (tidal wave). E. Dicrotic pulse with peaks in systole and diastole. This waveform may be seen in patients with sepsis or during intraaortic balloon counterpulsation with inflation just after the dicrotic notch. (From KChatterjee, W Parmley [eds]: *Cardiology: An Illustrated Text/Reference*. Philadelphia, Gower Medical Publishers, 1991.)

appreciated in patients on intraaortic balloon counterpulsation (IABP), in whom the second pulse is diastolic in timing.

Pulsus paradoxus refers to a fall in systolic pressure >10 mmHg with inspiration that is seen in patients with pericardial tamponade but also is described in those with massive pulmonary embolism, hemorrhagic shock, severe obstructive lung disease, and tension pneumothorax. Pulsus paradoxus is measured by noting the difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each heartbeat, independent of the respiratory phase. Between these two pressures, the Korotkoff sounds are heard only intermittently and during

expiration. The cuff pressure must be decreased slowly to appreciate the finding. It can be difficult to measure pulsus paradoxus in patients with tachycardia, atrial fibrillation, or tachypnea. A pulsus paradoxus may be palpable at the brachial artery or femoral artery level when the pressure difference exceeds 15 mmHg. The inspiratory fall in systolic pressure is an exaggerated consequence of interventricular dependence.

Pulsus alternans, in contrast, is defined by beat-to-beat variability of pulse amplitude. It is present only when every other phase I Korotkoff sound is audible as the cuff pressure is lowered slowly, typically in a patient with a regular heart rhythm and independent of the respiratory cycle. Pulsus alternans is seen in patients with severe left ventricular systolic dysfunction and is thought to be due to cyclic changes in intracellular calcium and action potential duration. When pulsus alternans is associated with electrocardiographic T-wave alternans, the risk for an arrhythmic event appears to be increased.

Ascending aortic aneurysms can rarely be appreciated as a pulsatile mass in the right parasternal area. Appreciation of a prominent abdominal aortic pulse should prompt noninvasive imaging for better characterization. Femoral and/or popliteal artery aneurysms should be sought in patients with abdominal aortic aneurysm disease.

The level of a claudication-producing arterial obstruction can often be identified on physical examination (Fig. 9-3). For example, in a patient with calf claudication, a decrease in pulse amplitude between the common femoral and popliteal arteries will localize the obstruction to the level of the superficial femoral artery, although inflow obstruction above the level of the common femoral artery may coexist. Auscultation for carotid, subclavian, abdominal aortic, and femoral artery bruits should be routine. However, the correlation between the presence of a bruit and the degree of vascular obstruction is poor. A cervical bruit is a weak

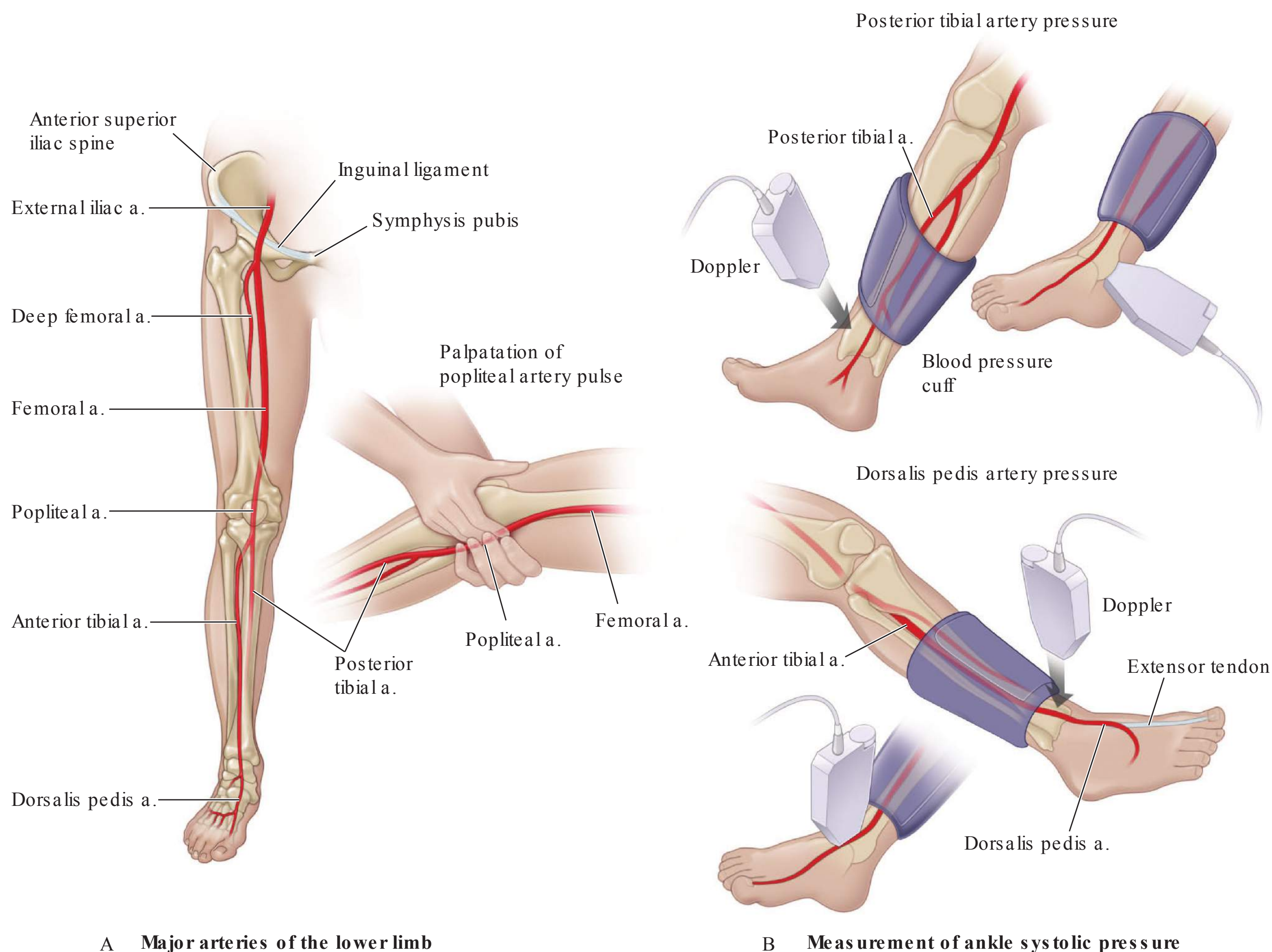


FIGURE 9-3

A. Anatomy of the major arteries of the leg. B. Measurement of the ankle systolic pressure. (From NAKhan et al: JAMA295:536, 2006.)

indicator of the degree of carotid artery stenosis; the absence of a bruit does not exclude the presence of significant luminal obstruction. If a bruit extends into diastole or if a thrill is present, the obstruction is usually severe. Another cause of an arterial bruit is an arteriovenous fistula with enhanced flow.

The likelihood of significant lower extremity peripheral arterial disease increases with typical symptoms of claudication, cool skin, abnormalities on pulse examination, or the presence of a vascular bruit. Abnormal pulse oximetry (a $>2\%$ difference between finger and toe oxygen saturation) can be used to detect lower extremity peripheral arterial disease and is comparable in its performance characteristics to the ankle-brachial index.

Inspection and palpation of the heart

The left ventricular apex beat may be visible in the midclavicular line at the fifth intercostal space in thin-chested adults. Visible pulsations anywhere other than this expected location are abnormal. The left anterior chest wall may heave in patients with an enlarged or hyperdynamic left or right ventricle. As noted previously, a visible right upper parasternal pulsation may be suggestive of ascending aortic aneurysm disease. In thin, tall patients and patients with advanced obstructive lung disease and flattened diaphragms, the cardiac impulse may be visible in the epigastrium and should be distinguished from a pulsatile liver edge.

Palpation of the heart begins with the patient in the supine position at 30° and can be enhanced by placing the patient in the left lateral decubitus position. The normal left ventricular impulse is less than 2 cm in diameter and moves quickly away from the fingers; it is better appreciated at end expiration, with the heart closer to the anterior chest wall. Characteristics such as size, amplitude, and rate of force development should be noted.

Enlargement of the left ventricular cavity is manifested by a leftward and downward displacement of an enlarged apex beat. A sustained apex beat is a sign of pressure overload, such as that which may be present in patients with AS or chronic hypertension. A palpable presystolic impulse corresponds to the fourth heart sound (S_4) and is indicative of reduced left ventricular compliance and the forceful contribution of atrial contraction to ventricular filling. A palpable third sound (S_3), which is indicative of a rapid early filling wave in patients with heart failure, may be present even when the gallop itself is not audible. A large left ventricular aneurysm may sometimes be palpable as an ectopic impulse, discrete from the apex beat. HOCM may very rarely cause a triple cadence beat at the apex with contributions from a palpable S_4 and the two components of the bisferiens systolic pulse.

Right ventricular pressure or volume overload may create a sternal lift. Signs of either TR (cv waves in the jugular venous pulse) and/or pulmonary arterial hypertension (a loud single or palpable P_2) would be confirmatory. The right ventricle can enlarge to the extent that left-sided events cannot be appreciated. A zone of retraction between the right and left ventricular impulses sometimes can be appreciated in patients with right ventricle pressure or volume overload when they are placed in the left lateral decubitus position. Systolic and diastolic thrills signify turbulent and high-velocity blood flow. Their locations help identify the origin of heart murmurs.

CARDIAC AUSCULTATION

Heart sounds

Ventricular systole is defined by the interval between the first (S_1) and second (S_2) heart sounds (Fig. 9-4). The first heart sound (S_1) includes mitral and tricuspid valve

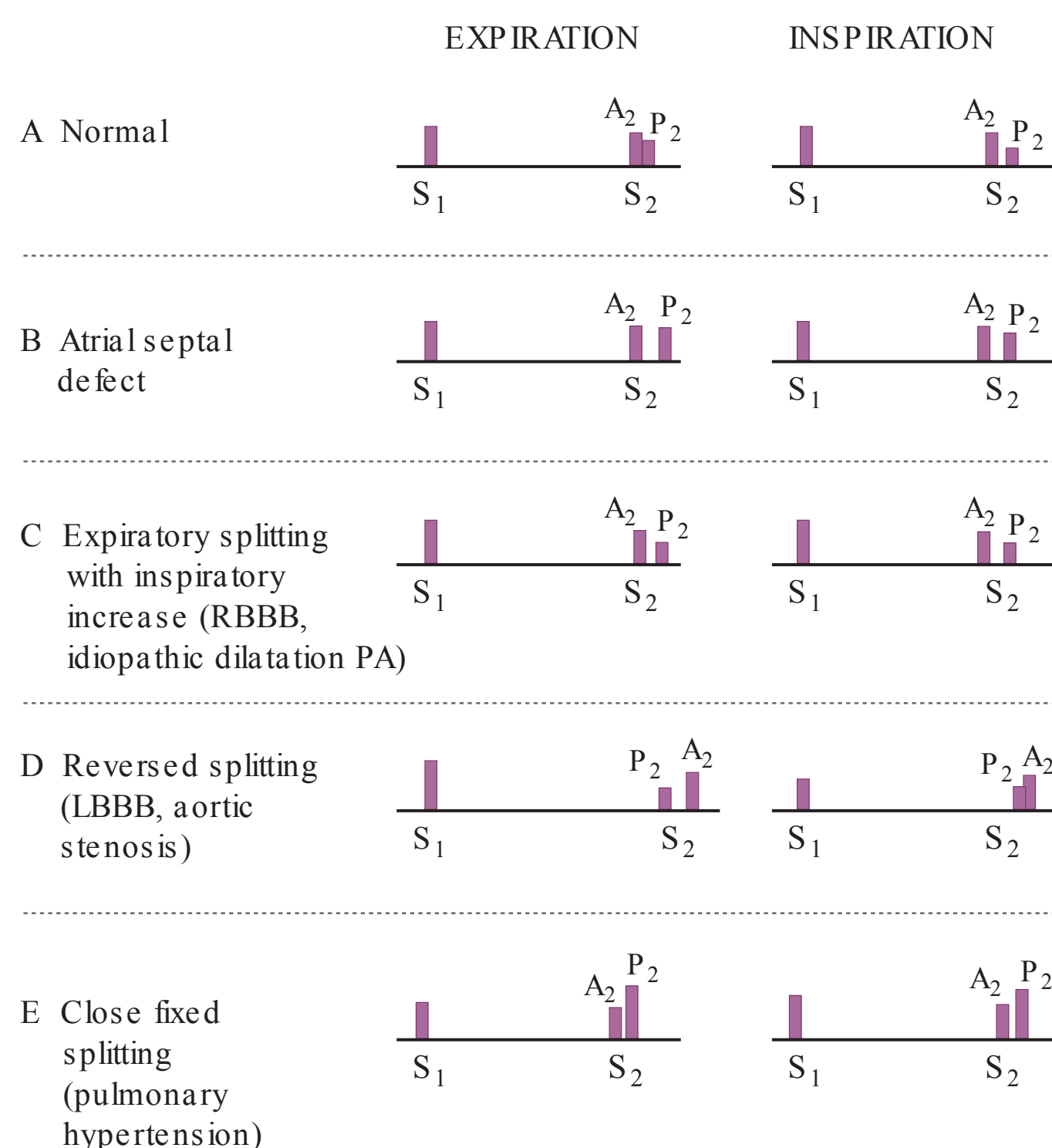


FIGURE 9-4

Heart sounds. A. Normal. S_1 , first heart sound; S_2 , second heart sound; A_2 , aortic component of the second heart sound; P_2 , pulmonary component of the second heart sound. B. Atrial septal defect with fixed splitting of S_2 . C. Physiologic but wide splitting of S_2 with right bundle branch block (RBBB). PA, pulmonary artery. D. Reversed or paradoxical splitting of S_2 with left bundle branch block (LBBB). E. Narrow splitting of S_2 with pulmonary hypertension. (From NO Fowler: *Diagnosis of Heart Disease*. New York, Springer-Verlag, 1991, p 31.)

closure. Normal splitting can be appreciated in young patients and those with right bundle branch block, in whom tricuspid valve closure is relatively delayed. The intensity of S_1 is determined by the distance over which the anterior leaflet of the mitral valve must travel to return to its annular plane, leaflet mobility, left ventricular contractility, and the PR interval. S_1 is classically loud in the early phases of rheumatic mitral stenosis (MS) and in patients with hyperkinetic circulatory states or short PR intervals. S_1 becomes softer in the later stages of MS when the leaflets are rigid and calcified, after exposure to β -adrenergic receptor blockers, with long PR intervals, and with left ventricular contractile dysfunction. The intensity of heart sounds, however, can be reduced by any process that increases the distance between the stethoscope and the responsible cardiac event, including mechanical ventilation, obstructive lung disease, obesity, pneumothorax, and a pericardial effusion.

Aortic and pulmonic valve closure constitutes the second heart sound (S_2). With normal or physiologic splitting, the A_2 – P_2 interval increases with inspiration and narrows during expiration. This physiologic interval will widen with right bundle branch block because of the further delay in pulmonic valve closure and in patients with severe MR because of the premature closure of the aortic valve. An unusually narrowly split or even a singular S_2 is a feature of pulmonary arterial hypertension. Fixed splitting of S_2 , in which the A_2 – P_2 interval is wide and does not change during the respiratory cycle, occurs in patients with a secundum atrial septal defect. Reversed or paradoxical splitting refers to a pathologic delay in aortic valve closure, such as that which occurs in patients with left bundle branch block, right ventricular pacing, severe AS, HOCM, and acute myocardial ischemia. With reversed or paradoxical splitting, the individual components of S_2 are audible at end expiration, and their interval narrows with inspiration, the opposite of what would be expected under normal physiologic conditions. P_2 is considered loud when its intensity exceeds that of A_2 at the base, when it can be palpated in the area of the proximal main pulmonary artery (second left interspace), or when both components of S_2 can be appreciated at the lower left sternal border or apex. The intensity of A_2 and P_2 decreases with aortic and pulmonic stenosis, respectively. In these conditions, a single S_2 may result.

Systolic sounds

An ejection sound is a high-pitched early systolic sound that corresponds in timing to the upstroke of the carotid pulse. It usually is associated with congenital bicuspid aortic or pulmonic valve disease; however, ejection sounds are also sometimes audible in patients with isolated aortic or pulmonary root dilation and

normal semilunar valves. The ejection sound that accompanies bicuspid aortic valve disease becomes softer and then inaudible as the valve calcifies and becomes more rigid. The ejection sound that accompanies pulmonic stenosis (PS) moves closer to the first heart sound as the severity of the stenosis increases. In addition, the pulmonic ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. Ejection sounds are often heard more easily at the lower left sternal border than they are at the base. Nonejection sounds (clicks), which occur after the onset of the carotid upstroke, are related to MVP and may be single or multiple. The nonejection click may introduce a murmur. This click-murmur complex will move away from the first heart sound with maneuvers that increase ventricular preload, such as squatting. On standing, the click and murmur move closer to S_1 .

Diastolic sounds

The high-pitched opening snap (OS) of MS occurs after a very short interval after the second heart sound. The A_2 –OS interval is inversely proportional to the height of the left atrial–left ventricular diastolic pressure gradient. The intensity of both S_1 and the OS of MS decreases with progressive calcification and rigidity of the anterior mitral leaflets. The pericardial knock (PK) is also high-pitched and occurs slightly later than the OS, corresponding in timing to the abrupt cessation of ventricular expansion after tricuspid valve opening and to an exaggerated y descent seen in the jugular venous waveform in patients with constrictive pericarditis. A tumor plop is a lower-pitched sound that rarely can be heard in patients with atrial myxoma. It may be appreciated only in certain positions and arises from the diastolic prolapse of the tumor across the mitral valve.

The third heart sound (S_3) occurs during the rapid filling phase of ventricular diastole. It can be a normal finding in children, adolescents, and young adults; however, in older patients, it signifies heart failure. A left-sided S_3 is a low-pitched sound best heard over the left ventricular (LV) apex. A right-sided S_3 is usually better heard over the lower left sternal border and becomes louder with inspiration. A left-sided S_3 in patients with chronic heart failure is predictive of cardiovascular morbidity and mortality. Interestingly, an S_3 is equally prevalent among heart failure patients with and without LV systolic dysfunction.

The fourth heart sound (S_4) occurs during the atrial filling phase of ventricular diastole and indicates LV presystolic expansion. An S_4 is more common among patients who derive significant benefit from the atrial contribution to ventricular filling, such as those with chronic LV hypertrophy or active myocardial ischemia. An S_4 is not present with atrial fibrillation.

Cardiac murmurs

Heart murmurs result from audible vibrations that are caused by increased turbulence and are defined by their timing within the cardiac cycle. Not all murmurs are indicative of structural heart disease, and the accurate identification of a benign or functional systolic murmur often can obviate the need for additional testing in healthy subjects. The duration, frequency, configuration, and intensity of a heart murmur are dictated by the magnitude, variability, and duration of the responsible pressure difference between two cardiac chambers, the two ventricles, or the ventricles and their respective great arteries. The intensity of a heart murmur is graded on a scale of 1 to 6; a thrill is present with murmurs of grade 4 or greater intensity. Other attributes of the murmur that aid in its accurate identification include its location, radiation, and response to bedside maneuvers. Although clinicians can detect and correctly identify heart murmurs with only fair reliability, a careful and complete bedside examination usually can identify individuals with valvular heart disease for whom trans-thoracic echocardiography and clinical follow-up are indicated and exclude subjects for whom no further evaluation is necessary.

Systolic murmurs can be early, mid, late, or holosystolic in timing (**Fig. 9-5**). Acute severe MR results in a decrescendo early systolic murmur, the characteristics of which are related to the progressive attenuation of the left ventricular to left atrial pressure gradient during systole because of the steep and rapid rise in left atrial pressure in this context. Severe MR associated with posterior leaflet prolapse or flail radiates anteriorly and to the base, where it can be confused with the murmur of AS. MR that is due to anterior leaflet involvement radiates posteriorly and to the axilla. With acute TR in patients with normal pulmonary artery pressures, an early systolic murmur that may increase in intensity with inspiration may be heard at the left lower sternal border, with regurgitant cv waves visible in the jugular venous pulse.

A midsystolic murmur begins after S_1 and ends before S_2 ; it is typically crescendo-decrescendo in configuration. AS is the most common cause of a midsystolic murmur in an adult. It is often difficult to estimate the severity of the valve lesion on the basis of the physical examination findings, especially in older hypertensive patients with stiffened carotid arteries or patients with low cardiac output in whom the intensity of the systolic heart murmur is misleadingly soft. Examination findings consistent with severe AS would include parvus et tardus carotid upstrokes, a late-peaking grade 3 or greater midsystolic murmur, a soft A_2 , a sustained LV apical impulse, and an S_4 . It is sometimes difficult to distinguish aortic sclerosis from more advanced degrees of valve stenosis. The former is defined by focal

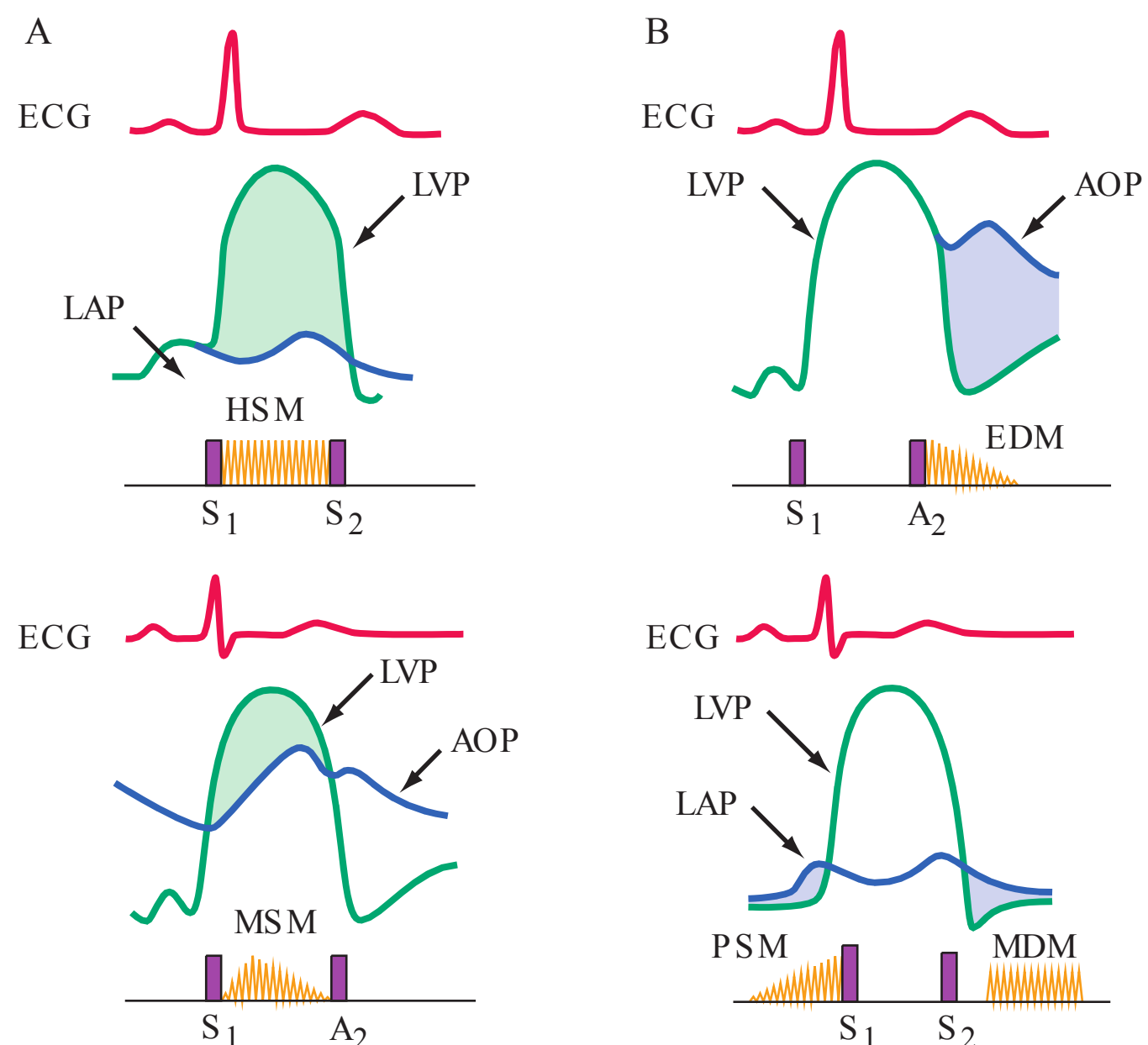


FIGURE 9-5

A. Top. Graphic representation of the systolic pressure difference (green shaded area) between left ventricle and left atrium with phonocardiographic recording of a holosystolic murmur (HSM) indicative of mitral regurgitation. ECG, electrocardiogram; LAP, left atrial pressure; LVP, left ventricular pressure; S_1 , first heart sound; S_2 , second heart sound. Bottom. Graphic representation of the systolic pressure gradient (green shaded area) between left ventricle and aorta in patient with aortic stenosis. A midsystolic murmur (MSM) with a crescendo-decrescendo configuration is recorded. AOP, aortic pressure. B. Top. Graphic representation of the diastolic pressure difference between the aorta and left ventricle (blue shaded area) in a patient with aortic regurgitation, resulting in a decrescendo, early diastolic murmur (EDM) beginning with A_2 . Bottom. Graphic representation of the diastolic left atrial–left ventricular gradient (blue areas) in a patient with mitral stenosis with a mid-diastolic murmur (MDM) and late presystolic murmurs (PSM).

thickening and calcification of the aortic valve leaflets that is not severe enough to result in obstruction. These valve changes are associated with a Doppler jet velocity across the aortic valve of 2.5 m/s or less. Patients with aortic sclerosis can have grade 2 or 3 midsystolic murmurs identical in their acoustic characteristics to the murmurs heard in patients with more advanced degrees of AS. Other causes of a midsystolic heart murmur include pulmonic valve stenosis (with or without an ejection sound), HOCM, increased pulmonary blood flow in patients with a large atrial septal defect and left-to-right shunting, and several states associated with accelerated blood flow in the absence of structural heart disease, such as fever, thyrotoxicosis, pregnancy, anemia, and normal childhood/adolescence.

The murmur of HOCM has features of both obstruction to LV outflow and MR, as would be expected from knowledge of the pathophysiology of this condition.

The systolic murmur of HOCM usually can be distinguished from other causes on the basis of its response to bedside maneuvers, including Valsalva, passive leg raising, and standing/squatting. In general, maneuvers that decrease LV preload (or increase LV contractility) will cause the murmur to intensify, whereas maneuvers that increase LV preload or afterload will cause a decrease in the intensity of the murmur. Accordingly, the systolic murmur of HOCM becomes louder during the strain phase of the Valsalva maneuver and after standing quickly from a squatting position. The murmur becomes softer with passive leg raising and when squatting. The murmur of AS is typically loudest in the second right interspace with radiation into the carotids, whereas the murmur of HOCM is best heard between the lower left sternal border and the apex. The murmur of PS is best heard in the second left interspace. The midsystolic murmur associated with enhanced pulmonic blood flow in the setting of a large atrial septal defect (ASD) is usually loudest at the mid-left sternal border.

A late systolic murmur, heard best at the apex, indicates MVP. As previously noted, the murmur may or may not be introduced by a nonejection click. Differential radiation of the murmur, as previously described, may

help identify the specific leaflet involved by the myxomatous process. The click-murmur complex behaves in a manner directionally similar to that demonstrated by the murmur of HOCM during the Valsalva and stand/squat maneuvers (**Fig. 9-6**). The murmur of MVP can be identified by the accompanying nonejection click.

Holosystolic murmurs are plateau in configuration and reflect a continuous and wide pressure gradient between the left ventricle and left atrium with chronic MR, the left ventricle and right ventricle with a ventricular septal defect (VSD), and the right ventricle and right atrium with TR. In contrast to acute MR, in chronic MR the left atrium is enlarged and its compliance is normal or increased to the extent that there is little if any further increase in left atrial pressure from any increase in regurgitant volume. The murmur of MR is best heard over the cardiac apex. The intensity of the murmur increases with maneuvers that increase LV afterload, such as sustained hand grip. The murmur of a VSD (without significant pulmonary hypertension) is holosystolic and loudest at the mid-left sternal border, where a thrill is usually present. The murmur of TR is loudest at the lower left sternal border, increases in intensity with inspiration (Carvallo's sign), and is

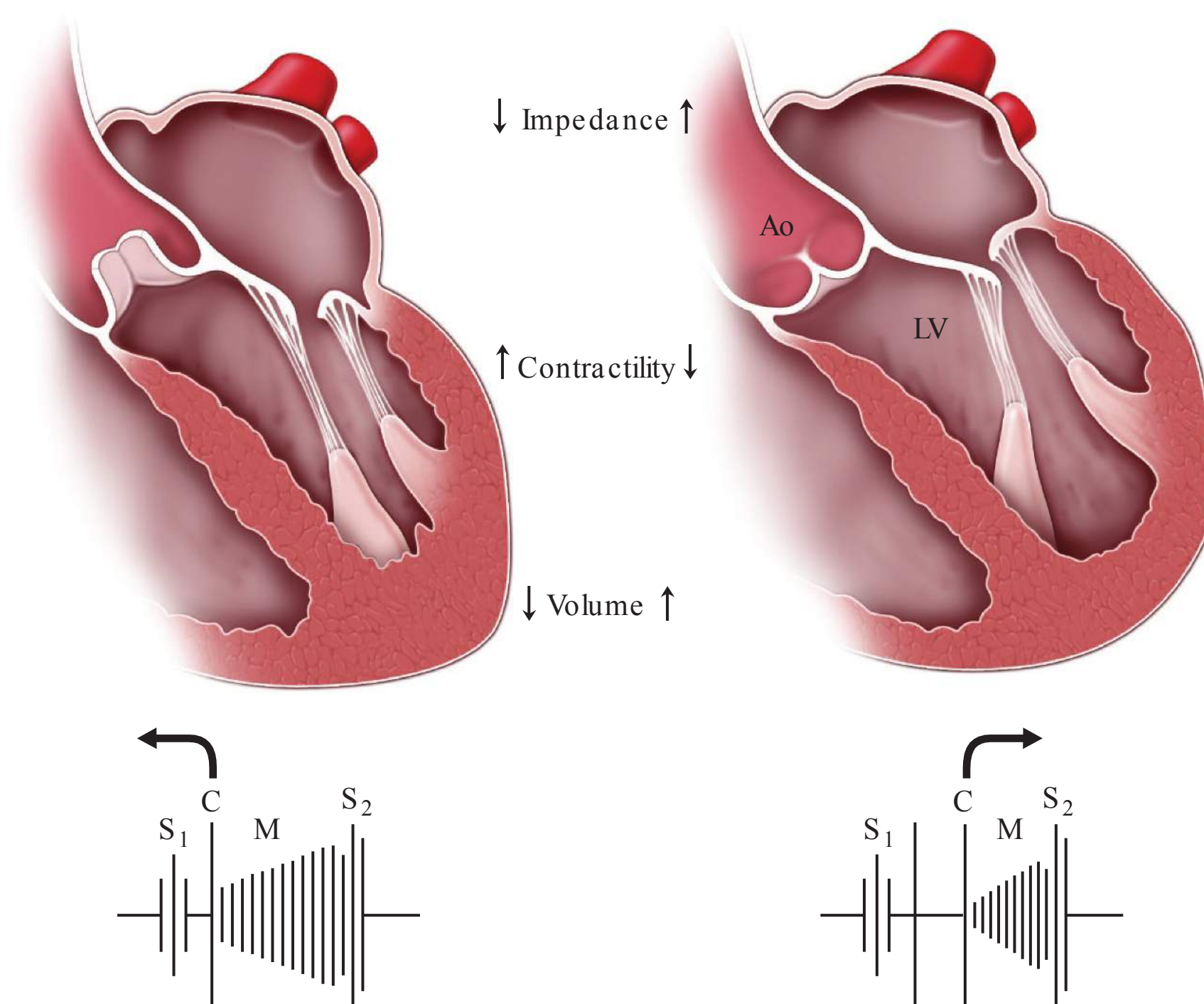


FIGURE 9-6

Behavior of the click (C) and murmur (M) of mitral valve prolapse with changes in loading (volume, impedance) and contractility. S₁, first heart sound; S₂, second heart sound. With standing (left side of figure), volume and impedance decrease, as a result of which the click and murmur move closer to S₁. With

squatting (right), the click and murmur move away from S₁ due to the increases in left ventricular volume and impedance (afterload). Ao, aorta; LV, left ventricle. (Adapted from RA O'Rourke, MH Crawford: *Curr Prob Cardiol* 1:9, 1976.)

accompanied by visible cv waves in the jugular venous wave form and, on occasion, by pulsatile hepatomegaly.

Diastolic murmurs

In contrast to some systolic murmurs, diastolic heart murmurs always signify structural heart disease (Fig. 9-5). The murmur associated with acute, severe AR is relatively soft and of short duration because of the rapid rise in LV diastolic pressure and the progressive diminution of the aortic-LV diastolic pressure gradient. In contrast, the murmur of chronic severe AR is classically heard as a decrescendo, blowing diastolic murmur along the left sternal border in patients with primary valve pathology and sometimes along the right sternal border in patients with primary aortic root pathology. With chronic AR, the pulse pressure is wide and the arterial pulses are bounding in character. These signs of significant diastolic run-off are absent in the acute phase. The murmur of pulmonic regurgitation is also heard along the left sternal border. It is most commonly due to pulmonary hypertension and enlargement of the annulus of the pulmonic valve. S₂ is single and loud and may be palpable. There is a right ventricular/parasternal lift that is indicative of chronic right ventricular pressure overload. A less impressive murmur of PR is present after repair of tetralogy of Fallot or pulmonic valve atresia. In this postoperative setting, the murmur is softer and lower-pitched, and the severity of the accompanying pulmonic regurgitation can be underestimated significantly.

MS is the classic cause of a mid- to late diastolic murmur, which is best heard over the apex in the left lateral decubitus position, is low-pitched or rumbling, and is introduced by an OS in the early stages of the rheumatic disease process. Presystolic accentuation refers to an increase in the intensity of the murmur just before the first heart sound and occurs in patients with sinus rhythm. It is absent in patients with atrial fibrillation. The auscultatory findings in patients with rheumatic tricuspid stenosis typically are obscured by left-sided events, although they are similar in nature to those described in patients with MS. “Functional” mitral or tricuspid stenosis refers to the generation of mid-diastolic murmurs that are created by increased and accelerated transvalvular diastolic flow, even in the absence of valvular obstruction, in the setting of severe MR, severe TR, or a large ASD with left-to-right shunting. The Austin Flint murmur of chronic severe AR is a low-pitched mid- to late apical diastolic murmur that sometimes can be confused with MS. The Austin Flint murmur typically decreases in intensity after exposure to vasodilators, whereas the murmur of MS may be accompanied by an opening snap and also may increase in intensity after vasodilators because of the associated

increase in cardiac output. Unusual causes of a mid-diastolic murmur include atrial myxoma, complete heart block, and acute rheumatic mitral valvulitis.

Continuous murmur

A continuous murmur is predicated on a pressure gradient that persists between two cardiac chambers or blood vessels across systole and diastole. The murmurs typically begin in systole, envelop the second heart sound (S₂), and continue through some portion of diastole. They can often be difficult to distinguish from individual systolic and diastolic murmurs in patients with mixed valvular heart disease. The classic example of a continuous murmur is that associated with a PDA, which usually is heard in the second or third interspace at a slight distance from the sternal border. Other causes of a continuous murmur include a ruptured sinus of Valsalva aneurysm with creation of an aortic–right atrial or right ventricular fistula, a coronary or great vessel arteriovenous fistula, and an arteriovenous fistula constructed to provide dialysis access. There are two types of benign continuous murmurs. The cervical venous hum is heard in children or adolescents in the supraclavicular fossa. It can be obliterated with firm pressure applied to the diaphragm of the stethoscope, especially when the subject turns his or her head toward the examiner. The mammary soufflé of pregnancy relates to enhanced arterial blood flow through engorged breasts. The diastolic component of the murmur can be obliterated with firm pressure over the stethoscope.

Dynamic auscultation

Diagnostic accuracy can be enhanced by the performance of simple bedside maneuvers to identify heart murmurs and characterize their significance (Table 9-1). Except for the pulmonic ejection sound, right-sided events increase in intensity with inspiration and decrease with expiration; left-sided events behave oppositely (100% sensitivity, 88% specificity). As previously noted, the intensity of the murmurs associated with MR, VSD, and AR will increase in response to maneuvers that increase LV afterload, such as hand grip and vasopressors. The intensity of these murmurs will decrease after exposure to vasodilating agents. Squatting is associated with an abrupt increase in LV preload and afterload, whereas rapid standing results in a sudden decrease in preload. In patients with MVP, the click and murmur move away from the first heart sound with squatting because of the delay in onset of leaflet prolapse at higher ventricular volumes. With rapid standing, however, the click and murmur move closer to the first heart sound as prolapse occurs earlier

in systole at a smaller chamber dimension. The murmur of HOCM behaves similarly, becoming softer and shorter with squatting (95% sensitivity, 85% specificity) and longer and louder on rapid standing (95% sensitivity, 84% specificity). A change in the intensity of a systolic murmur in the first beat after a premature beat or in the beat after a long cycle length in patients with atrial fibrillation suggests valvular AS rather than MR, particularly in an older patient in whom the murmur of the AS may be well transmitted to the apex (Gallavardin effect). Of note, however, the systolic murmur of HOCM also increases in intensity in the beat after a premature beat. This increase in intensity of any LV outflow murmur in the beat after a premature beat relates to the combined effects of enhanced LV filling (from the longer diastolic period) and postextrasystolic potentiation of LV contractile function. In either instance,

forward flow will accelerate, causing an increase in the gradient across the LV outflow tract (dynamic or fixed) and a louder systolic murmur. In contrast, the intensity of the murmur of MR does not change in a postpremature beat, because there is relatively little change in the nearly constant LV to left atrial pressure gradient or further alteration in mitral valve flow. Bedside exercise can sometimes be performed to increase cardiac output and, secondarily, the intensity of both systolic and diastolic heart murmurs. Most left-sided heart murmurs decrease in intensity and duration during the strain phase of the Valsalva maneuver. The murmurs associated with MVP and HOCM are the two notable exceptions. The Valsalva maneuver also can be used to assess the integrity of the heart and vasculature in the setting of advanced heart failure.

Prosthetic heart valves

The first clue that prosthetic valve dysfunction may contribute to recurrent symptoms is frequently a change in the quality of the heart sounds or the appearance of a new murmur. The heart sounds with a bioprosthetic valve resemble those generated by native valves. A mitral bioprosthesis usually is associated with a grade 2 or 3 midsystolic murmur along the left sternal border (created by turbulence across the valve struts as they project into the LV outflow tract) as well as by a soft mid-diastolic murmur that occurs with normal LV filling. This diastolic murmur often can be heard only in the left lateral decubitus position and after exercise. A high pitched or holosystolic apical murmur is indicative of pathologic MR due to a paravalvular leak and/or intra-annular bioprosthetic regurgitation from leaflet degeneration, for which additional imaging is usually indicated. Clinical deterioration can occur rapidly after the first expression of mitral bioprosthetic failure. A tissue valve in the aortic position is always associated with a grade 2 to 3 midsystolic murmur at the base or just below the suprasternal notch. A diastolic murmur of AR is abnormal in any circumstance. Mechanical valve dysfunction may first be suggested by a decrease in the intensity of either the opening or the closing sound. A high-pitched apical systolic murmur in patients with a mechanical mitral prosthesis and a diastolic decrescendo murmur in patients with a mechanical aortic prosthesis indicate paravalvular regurgitation. Patients with prosthetic valve thrombosis may present clinically with signs of shock, muffled heart sounds, and soft murmurs.

TABLE 9-1

EFFECTS OF PHYSIOLOGIC AND PHARMACOLOGIC INTERVENTIONS ON THE INTENSITY OF HEART MURMURS AND SOUNDS

Respiration Right-sided murmurs and sounds generally increase with inspiration, except for the PES. Left-sided murmurs and sounds are usually louder during expiration.

Valsalva maneuver Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HOCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. After release of the Valsalva maneuver, right-sided murmurs tend to return to control intensity earlier than do left-sided murmurs.

After VPB or AF Murmurs originating at normal or stenotic semilunar valves increase in the cardiac cycle after a VPB or in the cycle after a long cycle length in AF. By contrast, systolic murmurs due to AV valve regurgitation do not change, diminish (papillary muscle dysfunction), or become shorter (MVP).

Positional changes With standing, most murmurs diminish, with two exceptions being the murmur of HOCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With squatting, most murmurs become louder, but those of HOCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results.

Exercise Murmurs due to blood flow across normal or obstructed valves (e.g., PS, MS) become louder with both isotonic and submaximal isometric (hand grip) exercise. Murmurs of MR, VSD, and AR also increase with hand grip exercise. However, the murmur of HOCM often decreases with nearly maximum hand grip exercise. Left-sided S₄ and S₃ sounds are often accentuated by exercise, particularly when due to ischemic heart disease.

Abbreviations: AF, atrial fibrillation; AR, aortic regurgitation; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PES, pulmonic ejection sound; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VPB, ventricular premature beat; VSD, ventricular septal defect.

Pericardial disease

A pericardial friction rub is nearly 100% specific for the diagnosis of acute pericarditis, although the sensitivity of this finding is not nearly as high, because the rub

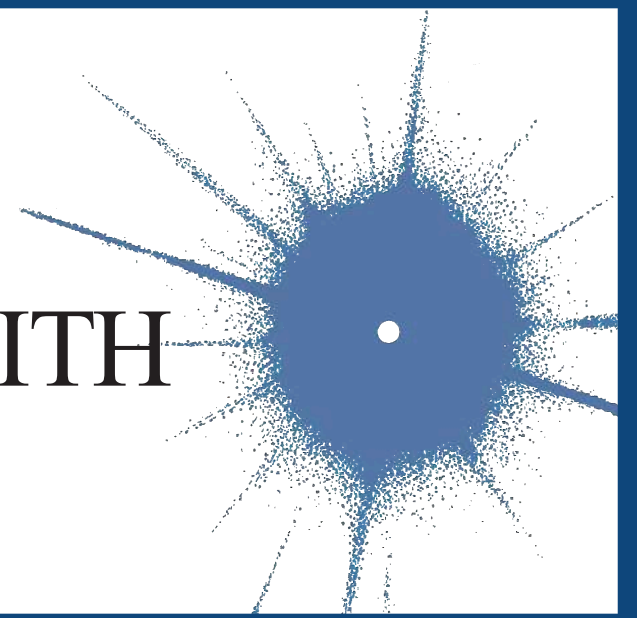
may come and go over the course of an acute illness or be very difficult to elicit. The rub is heard as a leathery or scratchy three-component or two-component sound, although it may be monophasic. Classically, the three components are ventricular systole, rapid early diastolic filling, and late presystolic filling after atrial contraction in patients in sinus rhythm. It is necessary to listen to the heart in several positions. Additional clues may be present from the history and 12-lead electrocardiogram. The rub typically disappears as the volume of any pericardial effusion increases. Pericardial tamponade can be diagnosed with a sensitivity of 98%, a specificity of 83%, and a positive likelihood ratio of 5.9

(95% confidence interval 2.4–14) by a pulsus paradoxus that exceeds 12 mmHg in a patient with a large pericardial effusion.

The findings on physical examination are integrated with the symptoms previously elicited with a careful history to construct an appropriate differential diagnosis and proceed with indicated imaging and laboratory assessment. The physical examination is an irreplaceable component of the diagnostic algorithm and in selected patients can inform prognosis. Educational efforts to improve clinician competence eventually may result in cost saving, particularly if the indications for imaging can be influenced by the examination findings.

CHAPTER 10

APPROACH TO THE PATIENT WITH A HEART MURMUR



Patrick T. O’Gara ■ Joseph Loscalzo

The differential diagnosis of a heart murmur begins with a careful assessment of its major attributes and response to bedside maneuvers. The history, clinical context, and associated physical examination findings provide additional clues by which the significance of a heart murmur can be established. Accurate bedside identification of a heart murmur can inform decisions regarding the indications for noninvasive testing and the need for referral to a cardiovascular specialist. Preliminary discussions can be held with the patient regarding antibiotic or rheumatic fever prophylaxis, the need to restrict various forms of physical activity, and the potential role for family screening.

Heart murmurs are caused by audible vibrations that are due to increased turbulence from accelerated blood flow through normal or abnormal orifices, flow through a narrowed or irregular orifice into a dilated vessel or chamber, or backward flow through an incompetent valve, ventricular septal defect, or patent ductus arteriosus. They traditionally are defined in terms of their timing within the cardiac cycle (**Fig. 10-1**). Systolic murmurs begin with or after the first heart sound (S_1) and terminate at or before the component (A_2 or P_2) of the second heart sound (S_2) that corresponds to their site of origin (left or right, respectively). Diastolic murmurs begin with or after the associated component of S_2 and end at or before the subsequent S_1 . Continuous murmurs are not confined to either phase of the cardiac cycle but instead begin in early systole and proceed through S_2 into all or part of diastole. The accurate timing of heart murmurs is the first step in their identification. The distinction between S_1 and S_2 and, therefore, systole and diastole is usually a straightforward process but can be difficult in the setting of a tachyarrhythmia, in which case the heart sounds can be distinguished by simultaneous

palpation of the carotid upstroke, which should closely follow S_1 .

Duration and character

The duration of a heart murmur depends on the length of time over which a pressure difference exists between two cardiac chambers, the left ventricle and the aorta, the right ventricle and the pulmonary artery, or the great vessels. The magnitude and variability of this pressure difference, coupled with the geometry and compliance of the involved chambers or vessels, dictate the velocity of flow; the degree of turbulence; and the resulting frequency, configuration, and intensity of the murmur. The diastolic murmur of chronic aortic regurgitation (AR) is a blowing, high-frequency event, whereas the murmur of mitral stenosis (MS), indicative of the left atrial–left ventricular diastolic pressure gradient, is a low-frequency event, heard as a rumbling sound with the bell of the stethoscope. The frequency components of a heart murmur may vary at different sites of auscultation. The coarse systolic murmur of aortic stenosis (AS) may sound higher pitched and more acoustically pure at the apex, a phenomenon eponymously referred to as the Gallavardin effect. Some murmurs may have a distinct or unusual quality, such as the “honking” sound appreciated in some patients with mitral regurgitation (MR) due to mitral valve prolapse (MVP).

The configuration of a heart murmur may be described as crescendo, decrescendo, crescendo-decrescendo, or plateau. The decrescendo configuration of the murmur of chronic AR (**Fig. 10-1E**) can be understood in terms of the progressive decline in the diastolic pressure gradient between the aorta and the left ventricle. The crescendo-decrescendo configuration of the murmur of AS reflects the changes

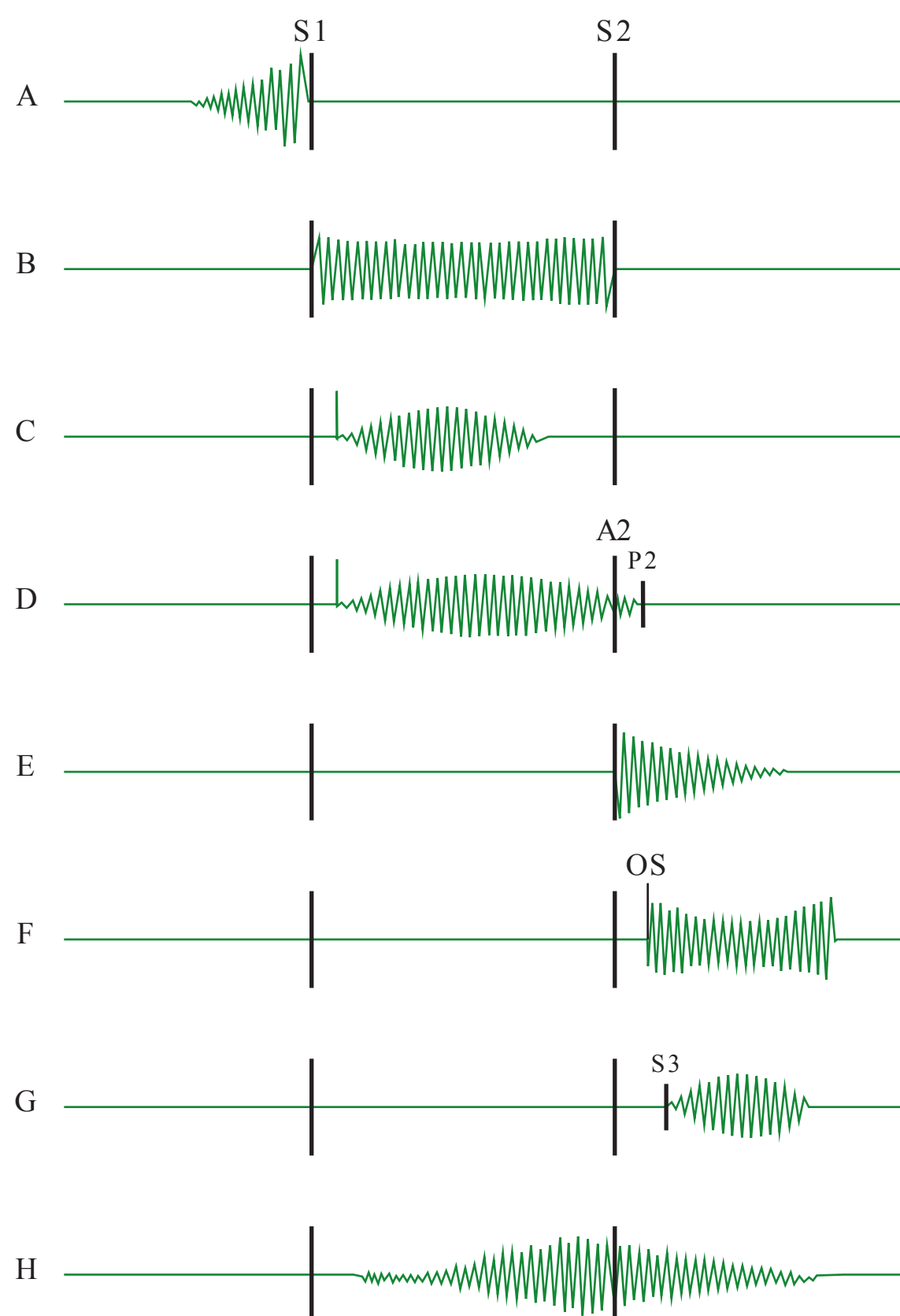


FIGURE 10-1

Diagram depicting principal heart murmurs. A. Presystolic murmur of mitral or tricuspid stenosis. B. Holosystolic (pansystolic) murmur of mitral or tricuspid regurgitation or of ventricular septal defect. C. Aortic ejection murmur beginning with an ejection click and fading before the second heart sound. D. Systolic murmur in pulmonic stenosis spilling through the aortic second sound, pulmonic valve closure being delayed. E. Aortic or pulmonary diastolic murmur. F. Long diastolic murmur of mitral stenosis after the opening snap (OS). G. Short mid-diastolic infow murmur after a third heart sound. H. Continuous murmur of patent ductus arteriosus. (Adapted from P Wood: *Diseases of the Heart and Circulation*, London, Eyre & Spottiswood, 1968. Permission granted courtesy of Antony and Julie Wood.)

in the systolic pressure gradient between the left ventricle and the aorta as ejection occurs, whereas the plateau configuration of the murmur of chronic MR (**Fig. 10-1B**) is consistent with the large and nearly constant pressure difference between the left ventricle and the left atrium.

Intensity

The intensity of a heart murmur is graded on a scale of 1–6 (or I–VI). A grade 1 murmur is very soft and is heard only with great effort. A grade 2 murmur is easily heard but not particularly loud. A grade 3 murmur is loud but is not accompanied by a palpable thrill over

the site of maximal intensity. A grade 4 murmur is very loud and is accompanied by a thrill. A grade 5 murmur is loud enough to be heard with only the edge of the stethoscope touching the chest, whereas a grade 6 murmur is loud enough to be heard with the stethoscope slightly off the chest. Murmurs of grade 3 or greater intensity usually signify important structural heart disease and indicate high blood flow velocity at the site of murmur production. Small ventricular septal defects (VSDs), for example, are accompanied by loud, usually grade 4 or greater, systolic murmurs as blood is ejected at high velocity from the left ventricle to the right ventricle. Low-velocity events, such as left-to-right shunting across an atrial septal defect (ASD), are usually silent. The intensity of a heart murmur may be diminished by any process that increases the distance between the intracardiac source and the stethoscope on the chest wall, such as obesity, obstructive lung disease, and a large pericardial effusion. The intensity of a murmur also may be misleadingly soft when cardiac output is reduced significantly or when the pressure gradient between the involved cardiac structures is low.

Location and radiation

Recognition of the location and radiation of the murmur helps facilitate its accurate identification (**Fig. 10-2**). Adventitious sounds, such as a systolic click or diastolic snap, or abnormalities of S₁ or S₂ may provide additional clues. Careful attention to the characteristics of the murmur and other heart sounds during the respiratory cycle and the performance of simple bedside maneuvers complete the auscultatory examination. These features, along with recommendations for further testing, are discussed below in the context of

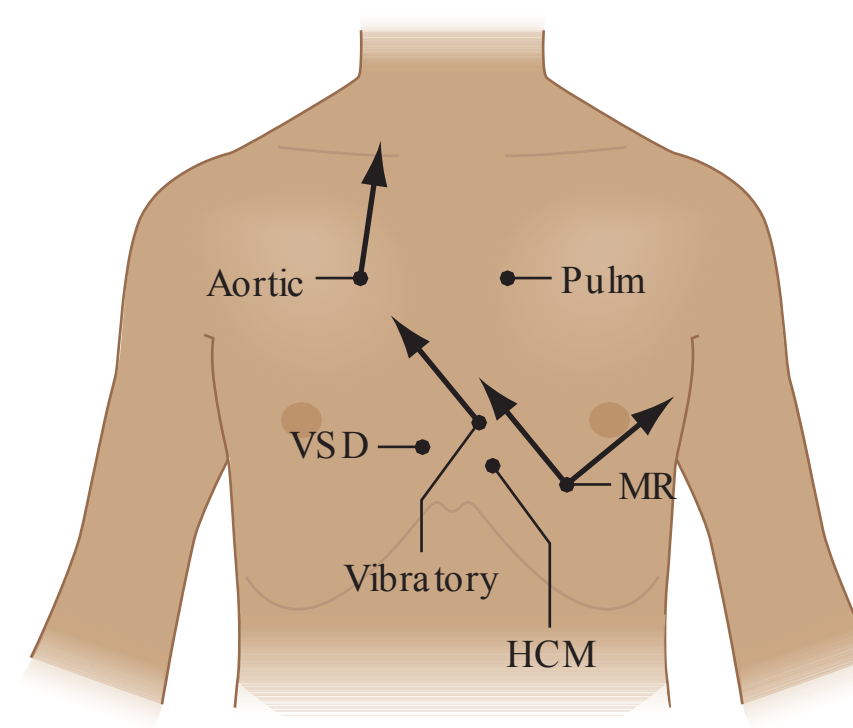


FIGURE 10-2

Maximal intensity and radiation of six isolated systolic murmurs. HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; Pulm, pulmonary stenosis; Aortic, aortic stenosis; VSD, ventricular septal defect. (From JB Barlow: *Perspectives on the Mitral Valve*. Philadelphia, FADavis, 1987, p 140.)

TABLE 10-1

PRINCIPAL CAUSES OF HEART MURMURS	
Systolic Murmurs	
Early systolic	
Mitral	
Acute MR	
VSD	
Muscular	
Nonrestrictive with pulmonary hypertension	
Tricuspid	
TR with normal pulmonary artery pressure	
Mid-systolic	
Aortic	
Obstructive	
Supravalvular–supravalvular aortic stenosis, coarctation of the aorta	
Valvular–AS and aortic sclerosis	
Subvalvular–discrete, tunnel or HOCM	
Increased flow, hyperkinetic states, AR, complete heart block	
Dilation of ascending aorta, atheroma, aortitis	
Pulmonary	
Obstructive	
Supravalvular–pulmonary artery stenosis	
Valvular–pulmonic valve stenosis	
Subvalvular–infundibular stenosis (dynamic)	
Increased flow, hyperkinetic states, left-to-right shunt (e.g., ASD)	
Dilation of pulmonary artery	
Late systolic	
Mitral	
MVP, acute myocardial ischemia	
Tricuspid	
TVP	
Holosystolic	
Atrioventricular valve regurgitation (MR, TR)	
Left-to-right shunt at ventricular level (VSD)	
Early Diastolic Murmurs	
Aortic regurgitation	
Valvular: congenital (bicuspid valve), rheumatic deformity, endocarditis, prolapse, trauma, post-valvulotomy	
Dilation of valve ring: aorta dissection, annuloaortic ectasia, cystic medial degeneration, hypertension, ankylosing spondylitis	
Widening of commissures: syphilis	
Pulmonic regurgitation	
Valvular: post-valvulotomy, endocarditis, rheumatic fever, carcinoid	

TABLE 10-1

PRINCIPAL CAUSES OF HEART MURMURS	
Dilation of valve ring: pulmonary hypertension; Marfan syndrome	
Congenital: isolated or associated with tetralogy of Fallot, VSD, pulmonic stenosis	
Mid-Diastolic Murmurs	
Mitral	
Mitral stenosis	
Carey-Coombs murmur (mid-diastolic apical murmur in acute rheumatic fever)	
Increased flow across nonstenotic mitral valve (e.g., MR, VSD, PDA, high-output states, and complete heart block)	
Tricuspid	
Tricuspid stenosis	
Increased flow across nonstenotic tricuspid valve (e.g., TR, ASD, and anomalous pulmonary venous return)	
Left and right atrial tumors (myxoma)	
Severe AR (Austin Flint murmur)	
Continuous Murmurs	
Patent ductus arteriosus	Proximal coronary artery stenosis
Coronary AV fistula	Mammary souffle of pregnancy
Ruptured sinus of Valsalva aneurysm	Pulmonary artery branch stenosis
Aortic septal defect	Bronchial collateral circulation
Cervical venous hum	Small (restrictive) ASD with MS
Anomalous left coronary artery	Intercostal AV fistula

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; AV, arteriovenous; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; TR, tricuspid regurgitation; TVP, tricuspid valve prolapse; VSD, ventricular septal defect.

Source: E Braunwald, JK Perloff, in D Zipes et al (eds): Braunwald’s Heart Disease, 7th ed. Philadelphia, Elsevier, 2005; PJ Norton, RA O’Rourke, in E Braunwald, L Goldman (eds): Primary Cardiology, 2nd ed. Philadelphia, Elsevier, 2003.

specific systolic, diastolic, and continuous heart murmurs (Table 10-1).

SYSTOLIC HEART MURMURS

Early systolic murmurs

Early systolic murmurs begin with S₁ and extend for a variable period, ending well before S₂. Their causes are relatively few in number. Acute, severe MR into a normal-sized, relatively noncompliant left atrium results in an early, decrescendo systolic murmur best

heard at or just medial to the apical impulse. These characteristics reflect the progressive attenuation of the pressure gradient between the left ventricle and the left atrium during systole owing to the rapid rise in left atrial pressure caused by the sudden volume load into an unprepared, noncompliant chamber and contrast sharply with the auscultatory features of chronic MR. Clinical settings in which acute, severe MR occur include (1) papillary muscle rupture complicating acute myocardial infarction (MI) (**Chap. 41**), (2) rupture of chordae tendineae in the setting of myxomatous mitral valve disease (MVP, **Chap. 23**), (3) infective endocarditis (**Chap. 31**), and (4) blunt chest wall trauma.

Acute, severe MR from papillary muscle rupture usually accompanies an inferior, posterior, or lateral MI and occurs 2–7 days after presentation. It often is signaled by chest pain, hypotension, and pulmonary edema, but a murmur may be absent in up to 50% of cases. The posteromedial papillary muscle is involved 6 to 10 times more frequently than the anterolateral papillary muscle. The murmur is to be distinguished from that associated with post-MI ventricular septal rupture, which is accompanied by a systolic thrill at the left sternal border in nearly all patients and is holosystolic in duration. A new heart murmur after an MI is an indication for transthoracic echocardiography (TTE) (**Chap. 12**), which allows bedside delineation of its etiology and pathophysiologic significance. The distinction between acute MR and ventricular septal rupture also can be achieved with right heart catheterization, sequential determination of oxygen saturations, and analysis of the pressure waveforms (tall v wave in the pulmonary artery wedge pressure in MR). Post-MI mechanical complications of this nature mandate aggressive medical stabilization and prompt referral for surgical repair.

Spontaneous chordal rupture can complicate the course of myxomatous mitral valve disease (MVP) and result in new-onset or “acute on chronic” severe MR. MVP may occur as an isolated phenomenon, or the lesion may be part of a more generalized connective tissue disorder as seen, for example, in patients with Marfan syndrome. Acute, severe MR as a consequence of infective endocarditis results from destruction of leaflet tissue, chordal rupture, or both. Blunt chest wall trauma is usually self-evident but may be disarmingly trivial; it can result in papillary muscle contusion and rupture, chordal detachment, or leaflet avulsion. TTE is indicated in all cases of suspected acute, severe MR to define its mechanism and severity, delineate left ventricular size and systolic function, and provide an assessment of suitability for primary valve repair.

A congenital, small muscular VSD (**Chap. 22**) may be associated with an early systolic murmur. The defect closes progressively during septal contraction, and thus, the murmur is confined to early systole. It is localized

to the left sternal border (**Fig. 10-2**) and is usually of grade 4 or 5 intensity. Signs of pulmonary hypertension or left ventricular volume overload are absent. Anatomically large and uncorrected VSDs, which usually involve the membranous portion of the septum, may lead to pulmonary hypertension. The murmur associated with the left-to-right shunt, which earlier may have been holosystolic, becomes limited to the first portion of systole as the elevated pulmonary vascular resistance leads to an abrupt rise in right ventricular pressure and an attenuation of the interventricular pressure gradient during the remainder of the cardiac cycle. In such instances, signs of pulmonary hypertension (right ventricular lift, loud and single or closely split S_2) may predominate. The murmur is best heard along the left sternal border but is softer. Suspicion of a VSD is an indication for TTE.

Tricuspid regurgitation (TR) with normal pulmonary artery pressures, as may occur with infective endocarditis, may produce an early systolic murmur. The murmur is soft (grade 1 or 2), is best heard at the lower left sternal border, and may increase in intensity with inspiration (Carvallo’s sign). Regurgitant “c-v” waves may be visible in the jugular venous pulse. TR in this setting is not associated with signs of right heart failure.

Mid-systolic murmurs

Mid-systolic murmurs begin at a short interval after S_1 , end before S_2 (**Fig. 10-1C**), and are usually crescendo-decrescendo in configuration. Aortic stenosis is the most common cause of a mid-systolic murmur in an adult. The murmur of AS is usually loudest to the right of the sternum in the second intercostal space (aortic area, **Fig. 10-2**) and radiates into the carotids. Transmission of the mid-systolic murmur to the apex, where it becomes higher-pitched, is common (Gallavardin effect; see above).

Differentiation of this apical systolic murmur from MR can be difficult. The murmur of AS will increase in intensity, or become louder, in the beat after a premature beat, whereas the murmur of MR will have constant intensity from beat to beat. The intensity of the AS murmur also varies directly with the cardiac output. With a normal cardiac output, a systolic thrill and a grade 4 or higher murmur suggest severe AS. The murmur is softer in the setting of heart failure and low cardiac output. Other auscultatory findings of severe AS include a soft or absent A_2 , paradoxical splitting of S_2 , an apical S_4 , and a late-peaking systolic murmur. In children, adolescents, and young adults with congenital valvular AS, an early ejection sound (click) is usually audible, more often along the left sternal border than at the base. Its presence signifies a flexible, noncalcified bicuspid valve (or one of its variants) and localizes

the left ventricular outflow obstruction to the valvular (rather than sub- or supra-valvular) level.

Assessment of the volume and rate of rise of the carotid pulse can provide additional information. A small and delayed upstroke (*parvus et tardus*) is consistent with severe AS. The carotid pulse examination is less discriminatory, however, in older patients with stiffened arteries. The electrocardiogram (ECG) shows signs of left ventricular hypertrophy (LVH) as the severity of the stenosis increases. TTE is indicated to assess the anatomic features of the aortic valve, the severity of the stenosis, left ventricular size, wall thickness and function, and the size and contour of the aortic root and proximal ascending aorta.

The obstructive form of hypertrophic cardiomyopathy (HOCM) is associated with a mid-systolic murmur that is usually loudest along the left sternal border or between the left lower sternal border and the apex (**Chap. 27, Fig. 10-2**). The murmur is produced by both dynamic left ventricular outflow tract obstruction and MR, and thus, its configuration is a hybrid between ejection and regurgitant phenomena. The intensity of the murmur may vary from beat to beat and after provocative maneuvers but usually does not exceed grade 3. The murmur classically will increase in intensity with maneuvers that result in increasing degrees of outflow tract obstruction, such as a reduction in preload or afterload (Valsalva, standing, vasodilators), or with an augmentation of contractility (inotropic stimulation). Maneuvers that increase preload (squatting, passive leg raising, volume administration) or afterload (squatting, vasopressors) or that reduce contractility (β -adrenoreceptor blockers) decrease the intensity of the murmur. In rare patients, there may be reversed splitting of S_2 . A sustained left ventricular apical impulse and an S_4 may be appreciated. In contrast to AS, the carotid upstroke is rapid and of normal volume. Rarely, it is bisferiens or bifid in contour (**see Fig. 9-2D**) due to mid-systolic closure of the aortic valve. LVH is present on the ECG, and the diagnosis is confirmed by TTE. Although the systolic murmur associated with MVP behaves similarly to that due to HOCM in response to the Valsalva maneuver and to standing/squatting (**Fig. 10-3**), these two lesions can be distinguished on the basis of their associated findings, such as the presence of LVH in HOCM or a nonejection click in MVP.

The mid-systolic, crescendo-decrescendo murmur of congenital pulmonic stenosis (PS, **Chap. 22**) is best appreciated in the second and third left intercostal spaces (pulmonic area) (**Figs. 10-2 and 10-4**). The duration of the murmur lengthens and the intensity of P_2 diminishes with increasing degrees of valvular stenosis (**Fig. 10-1D**). An early ejection sound, the intensity of which decreases with inspiration, is heard in younger

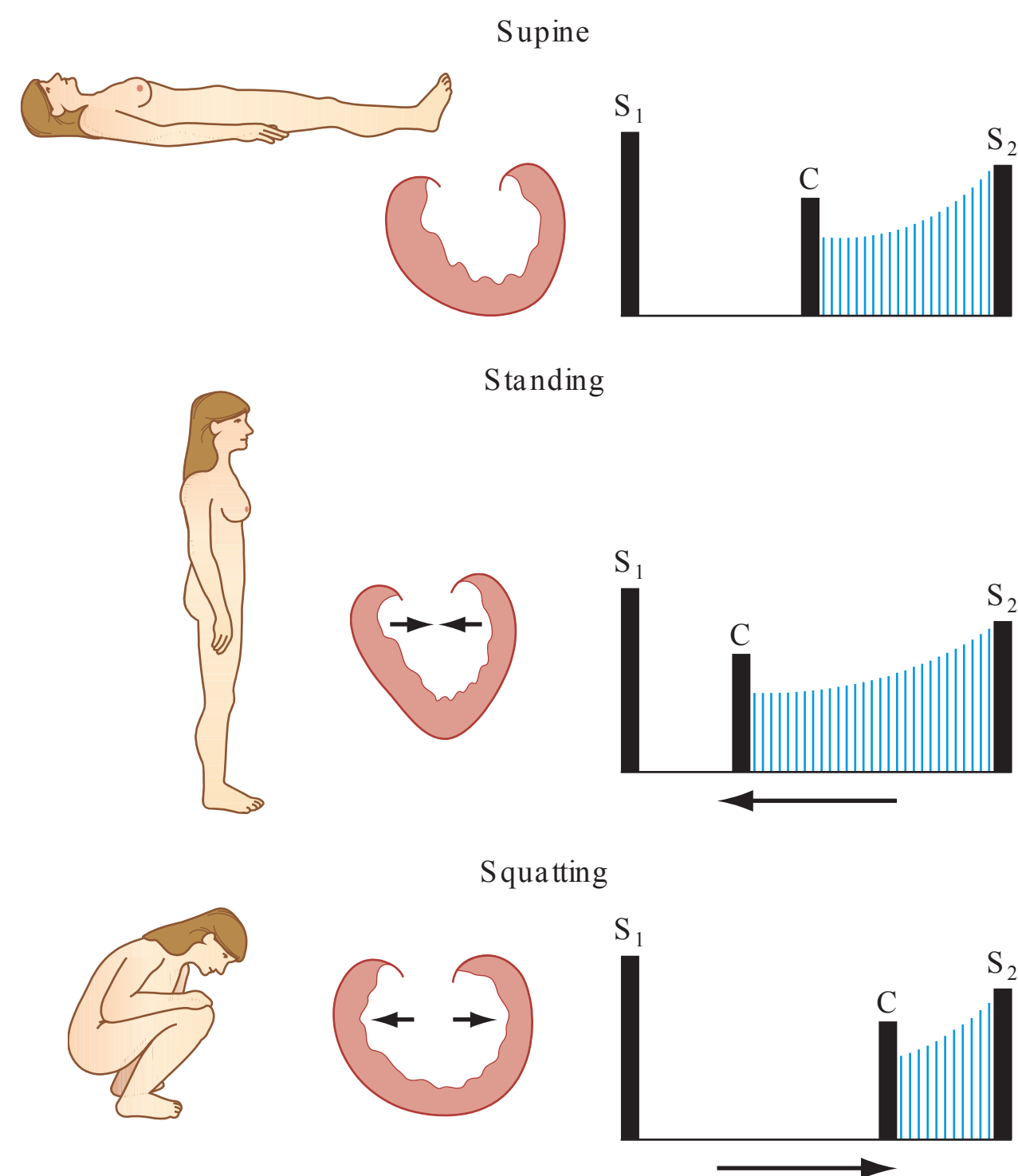


FIGURE 10-3

A mid-systolic nonejection sound (C) occurs in mitral valve prolapse and is followed by a late systolic murmur that crescendos to the second heart sound (S_2). Standing decreases venous return; the heart becomes smaller; C moves closer to the first heart sound (S_1), and the mitral regurgitant murmur has an earlier onset. With prompt squatting, venous return and afterload increase; the heart becomes larger; C moves toward S_2 ; and the duration of the murmur shortens. (From JA Shaver, JJ Leonard, DF Leon: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 13. Copyright, American Heart Association.)

patients. A parasternal lift and ECG evidence of right ventricular hypertrophy indicate severe pressure overload. If obtained, the chest x-ray may show poststenotic dilation of the main pulmonary artery. TTE is recommended for complete characterization.

Significant left-to-right intracardiac shunting due to an ASD (**Chap. 22**) leads to an increase in pulmonary blood flow and a grade 2–3 mid-systolic murmur at the middle to upper left sternal border attributed to increased flow rates across the pulmonic valve with fixed splitting of S_2 . Ostium secundum ASDs are the most common cause of these shunts in adults. Features suggestive of a primum ASD include the coexistence of MR due to a cleft anterior mitral valve leaflet and left axis deviation of the QRS complex on the ECG. With sinus venosus ASDs, the left-to-right shunt is usually not large enough to result in a systolic murmur, although the ECG may show abnormalities of sinus node function. A grade 2 or 3 mid-systolic murmur

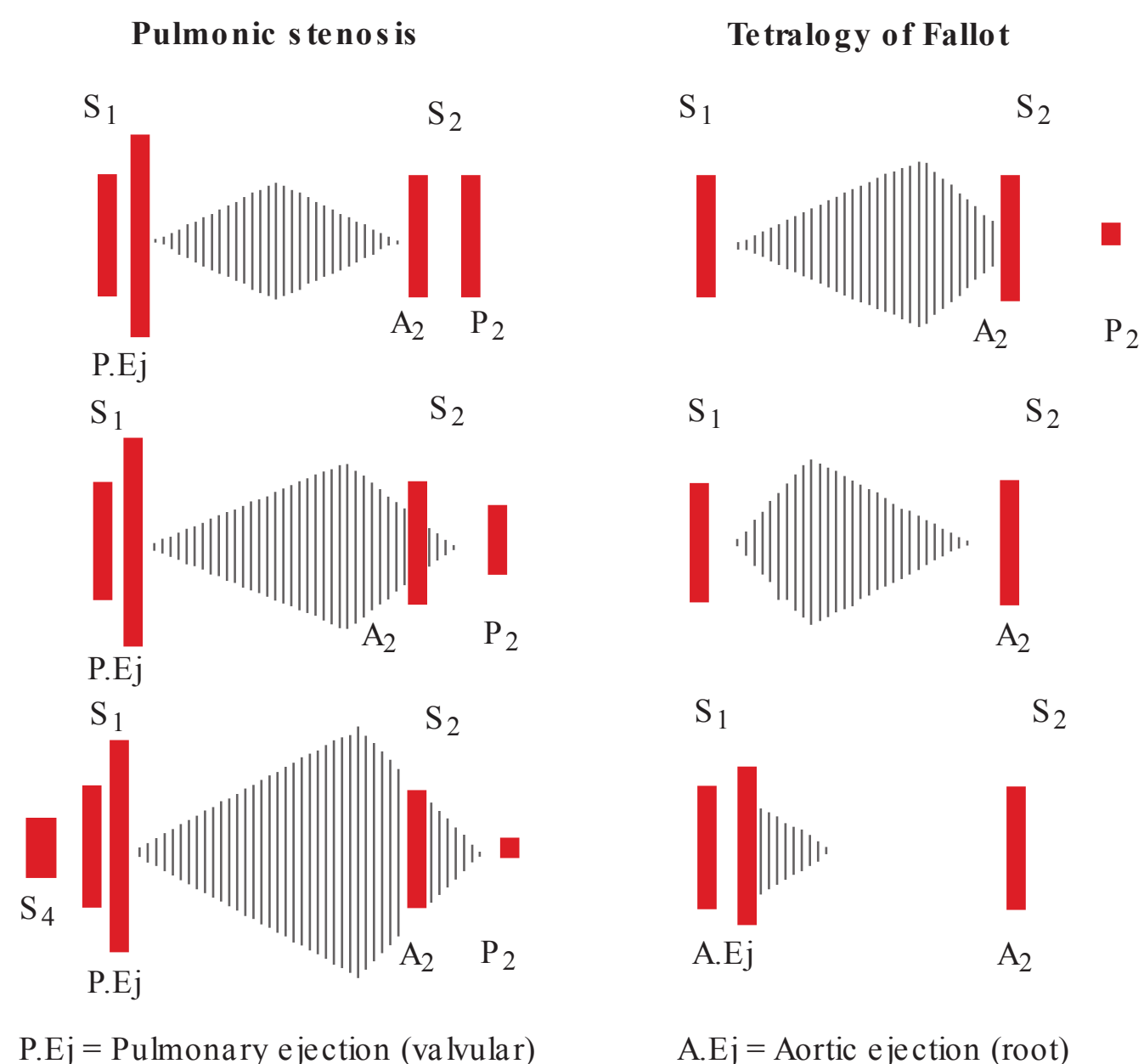


FIGURE 10-4

Left. In valvular pulmonic stenosis with intact ventricular septum, right ventricular systolic ejection becomes progressively longer, with increasing obstruction to flow. As a result, the murmur becomes longer and louder, enveloping the aortic component of the second heart sound (A_2). The pulmonic component (P_2) occurs later, and splitting becomes wider but more difficult to hear because A_2 is lost in the murmur and P_2 becomes progressively fainter and lower pitched. As the pulmonic gradient increases, the isometric contraction phase shortens until the pulmonic valve ejection sound fuses with the first heart sound (S_1). In severe pulmonic stenosis with concentric hypertrophy and decreasing right ventricular compliance, a fourth heart sound appears. Right. In tetralogy of Fallot with increasing obstruction at the pulmonic infundibular area, an increasing amount of right ventricular blood is shunted across the silent ventricular septal defect and flow across the obstructed outflow tract decreases. Therefore, with increasing obstruction the murmur becomes shorter, earlier, and fainter. P_2 is absent in severe tetralogy of Fallot. A large aortic root receives almost all cardiac output from both ventricular chambers, and the aorta dilates and is accompanied by a root ejection sound that does not vary with respiration. (From JAShaver, JJ Leonard, DF Leon: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 45. Copyright, American Heart Association.)

may also be heard best at the upper left sternal border in patients with idiopathic dilation of the pulmonary artery; a pulmonary ejection sound is also present in these patients. TTE is indicated to evaluate a grade 2 or 3 mid-systolic murmur when there are other signs of cardiac disease.

An isolated grade 1 or 2 mid-systolic murmur, heard in the absence of symptoms or signs of heart disease, is most often a benign finding for which no further evaluation, including TTE, is necessary. The most common

example of a murmur of this type in an older adult patient is the crescendo-decrescendo murmur of aortic valve sclerosis, heard at the second right interspace (**Fig. 10-2**). Aortic sclerosis is defined as focal thickening and calcification of the aortic valve to a degree that does not interfere with leaflet opening. The carotid upstrokes are normal, and electrocardiographic LVH is not present. A grade 1 or 2 mid-systolic murmur often can be heard at the left sternal border with pregnancy, hyperthyroidism, or anemia, physiologic states that are associated with accelerated blood flow. Still's murmur refers to a benign grade 2, vibratory or musical mid-systolic murmur at the mid or lower left sternal border in normal children and adolescents, best heard in the supine position (**Fig. 10-2**).

Late systolic murmurs

A late systolic murmur that is best heard at the left ventricular apex is usually due to MVP (**Chap. 23**). Often, this murmur is introduced by one or more nonejection clicks. The radiation of the murmur can help identify the specific mitral leaflet involved in the process of prolapse or flail. The term flail refers to the movement made by an unsupported portion of the leaflet after loss of its chordal attachment(s). With posterior leaflet prolapse or flail, the resultant jet of MR is directed anteriorly and medially, as a result of which the murmur radiates to the base of the heart and masquerades as AS. Anterior leaflet prolapse or flail results in a posteriorly directed MR jet that radiates to the axilla or left infrascapular region. Leaflet flail is associated with a murmur of grade 3 or 4 intensity that can be heard throughout the precordium in thin-chested patients. The presence of an S_3 or a short, rumbling mid-diastolic murmur due to enhanced flow signifies severe MR.

Bedside maneuvers that decrease left ventricular preload, such as standing, will cause the click and murmur of MVP to move closer to the first heart sound, as leaflet prolapse occurs earlier in systole. Standing also causes the murmur to become louder and longer. With squatting, left ventricular preload and afterload are increased abruptly, leading to an increase in left ventricular volume, and the click and murmur move away from the first heart sound as leaflet prolapse is delayed; the murmur becomes softer and shorter in duration (**Fig. 10-3**). As noted above, these responses to standing and squatting are directionally similar to those observed in patients with HOCM.

A late, apical systolic murmur indicative of MR may be heard transiently in the setting of acute myocardial ischemia; it is due to apical tethering and malcoaptation of the leaflets in response to structural and functional changes of the ventricle and mitral annulus. The intensity of the murmur varies as a function of left ventricular afterload and will increase in the setting of

hypertension. TTE is recommended for assessment of late systolic murmurs.

Holosystolic murmurs

(Figs. 10-1B and 10-5) Holosystolic murmurs begin with S_1 and continue through systole to S_2 . They are usually indicative of chronic mitral or tricuspid valve regurgitation or a VSD and warrant TTE for further characterization. The holosystolic murmur of chronic MR is best heard at the left ventricular apex and radiates to the axilla (Fig. 10-2); it is usually high-pitched and plateau in configuration because of the wide difference between left ventricular and left atrial pressure throughout systole. In contrast to acute MR, left atrial compliance is normal or even increased in chronic MR. As a result, there is only a small increase in left atrial pressure for any increase in regurgitant volume.

Several conditions are associated with chronic MR and an apical holosystolic murmur, including rheumatic scarring of the leaflets, mitral annular calcification, postinfarction left ventricular remodeling, and severe left ventricular chamber enlargement. The circumference of the mitral annulus increases as the left ventricle enlarges and leads to failure of leaflet coaptation with central MR in patients with dilated cardiomyopathy (Chap. 27). The severity of the MR is worsened by any

contribution from apical displacement of the papillary muscles and leaflet tethering (remodeling). Because the mitral annulus is contiguous with the left atrial endocardium, gradual enlargement of the left atrium from chronic MR will result in further stretching of the annulus and more MR; thus, “MR begets MR.” Chronic severe MR results in enlargement and leftward displacement of the left ventricular apex beat and, in some patients, a diastolic filling complex, as described previously.

The holosystolic murmur of chronic TR is generally softer than that of MR, is loudest at the left lower sternal border, and usually increases in intensity with inspiration (Carvallo’s sign). Associated signs include c-v waves in the jugular venous pulse, an enlarged and pulsatile liver, ascites, and peripheral edema. The abnormal jugular venous waveforms are the predominant finding and are seen very often in the absence of an audible murmur despite Doppler echocardiographic verification of TR. Causes of primary TR include myxomatous disease (prolapse), endocarditis, rheumatic disease, radiation, carcinoid, Ebstein’s anomaly, and chordal detachment as a complication of right ventricular endomyocardial biopsy. TR is more commonly a passive process that results secondarily from annular enlargement due to right ventricular dilatation in the face of volume or pressure overload.

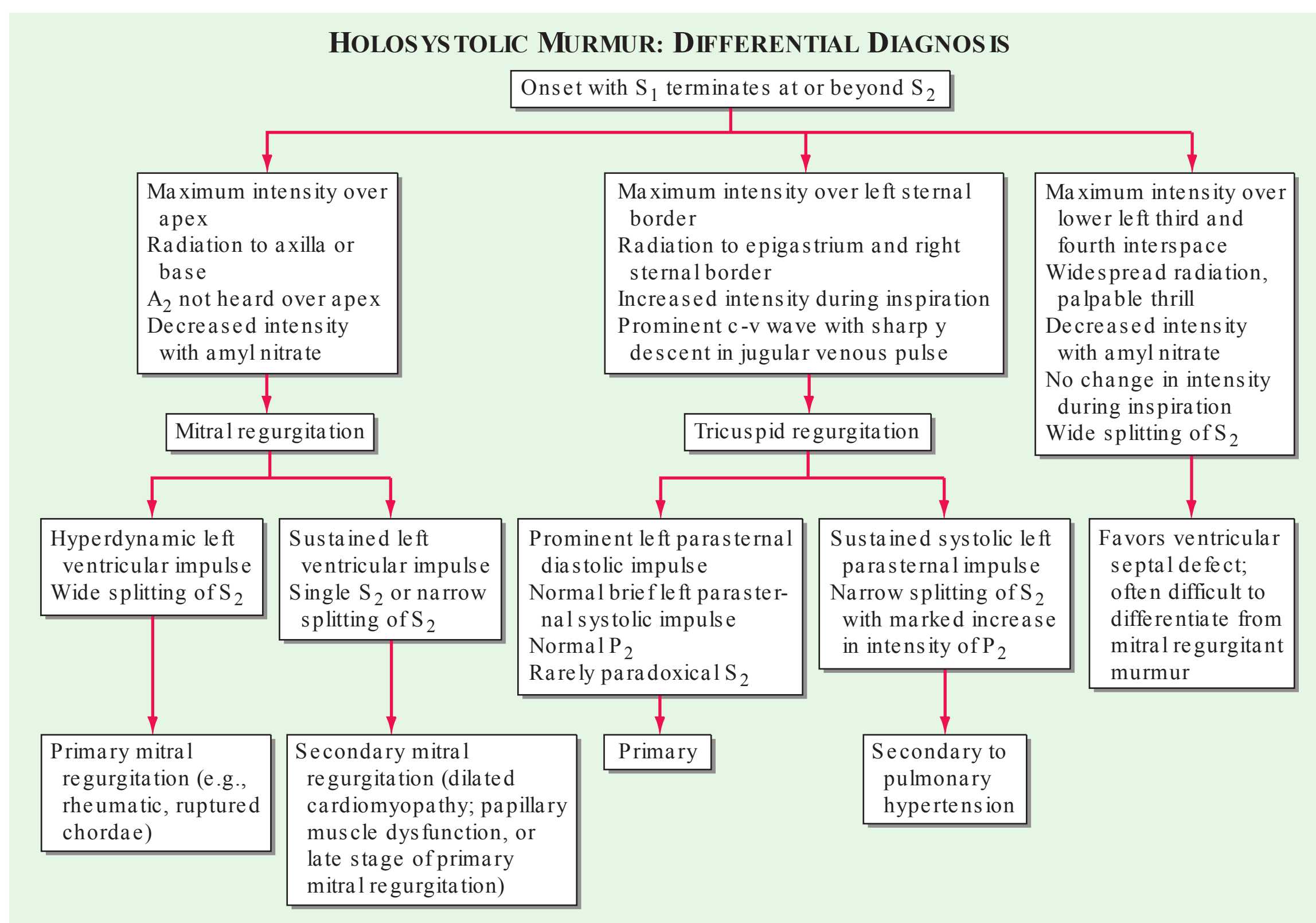


FIGURE 10-5

Differential diagnosis of a holosystolic murmur.

The holosystolic murmur of a VSD is loudest at the mid- to lower left sternal border (**Fig. 10-2**) and radiates widely. A thrill is present at the site of maximal intensity in the majority of patients. There is no change in the intensity of the murmur with inspiration. The intensity of the murmur varies as a function of the anatomic size of the defect. Small, restrictive VSDs, as exemplified by the *maladie de Roger*, create a very loud murmur due to the significant and sustained systolic pressure gradient between the left and right ventricles. With large defects, the ventricular pressures tend to equalize, shunt flow is balanced, and a murmur is not appreciated. The distinction between post-MI ventricular septal rupture and MR has been reviewed previously.

DIASTOLIC HEART MURMURS

Early diastolic murmurs

(**Fig. 10-1E**) Chronic AR results in a high-pitched, blowing, decrescendo, early to mid-diastolic murmur that begins after the aortic component of S_2 (A_2) and is best heard at the second right interspace (**Fig. 10-6**). The murmur may be soft and difficult to hear unless auscultation is performed with the patient leaning forward at end expiration. This maneuver brings the aortic root closer to the anterior chest wall. Radiation of the murmur may provide a clue to the cause of the AR. With primary valve disease, such as that due to congenital bicuspid disease, prolapse, or endocarditis, the diastolic murmur tends to radiate along the left sternal border, where it is often louder than appreciated in the second right interspace. When AR is caused by aortic

root disease, the diastolic murmur may radiate along the right sternal border. Diseases of the aortic root cause dilation or distortion of the aortic annulus and failure of leaflet coaptation. Causes include Marfan syndrome with aneurysm formation, annuloaortic ectasia, ankylosing spondylitis, and aortic dissection.

Chronic, severe AR also may produce a lower-pitched mid to late, grade 1 or 2 diastolic murmur at the apex (Austin Flint murmur), which is thought to reflect turbulence at the mitral inflow area from the admixture of regurgitant (aortic) and forward (mitral) blood flow (**Fig. 10-1G**). This lower-pitched, apical diastolic murmur can be distinguished from that due to MS by the absence of an opening snap and the response of the murmur to a vasodilator challenge. Lowering afterload with an agent such as amyl nitrite will decrease the duration and magnitude of the aortic–left ventricular diastolic pressure gradient, and thus, the Austin Flint murmur of severe AR will become shorter and softer. The intensity of the diastolic murmur of mitral stenosis (**Fig. 10-6**) may either remain constant or increase with afterload reduction because of the reflex increase in cardiac output and mitral valve flow.

Although AS and AR may coexist, a grade 2 or 3 crescendo-decrescendo mid-systolic murmur frequently is heard at the base of the heart in patients with isolated, severe AR and is due to an increased volume and rate of systolic flow. Accurate bedside identification of coexistent AS can be difficult unless the carotid pulse examination is abnormal or the mid-systolic murmur is of grade 4 or greater intensity. In the absence of heart failure, chronic severe AR is accompanied by several peripheral signs of significant diastolic run-off,

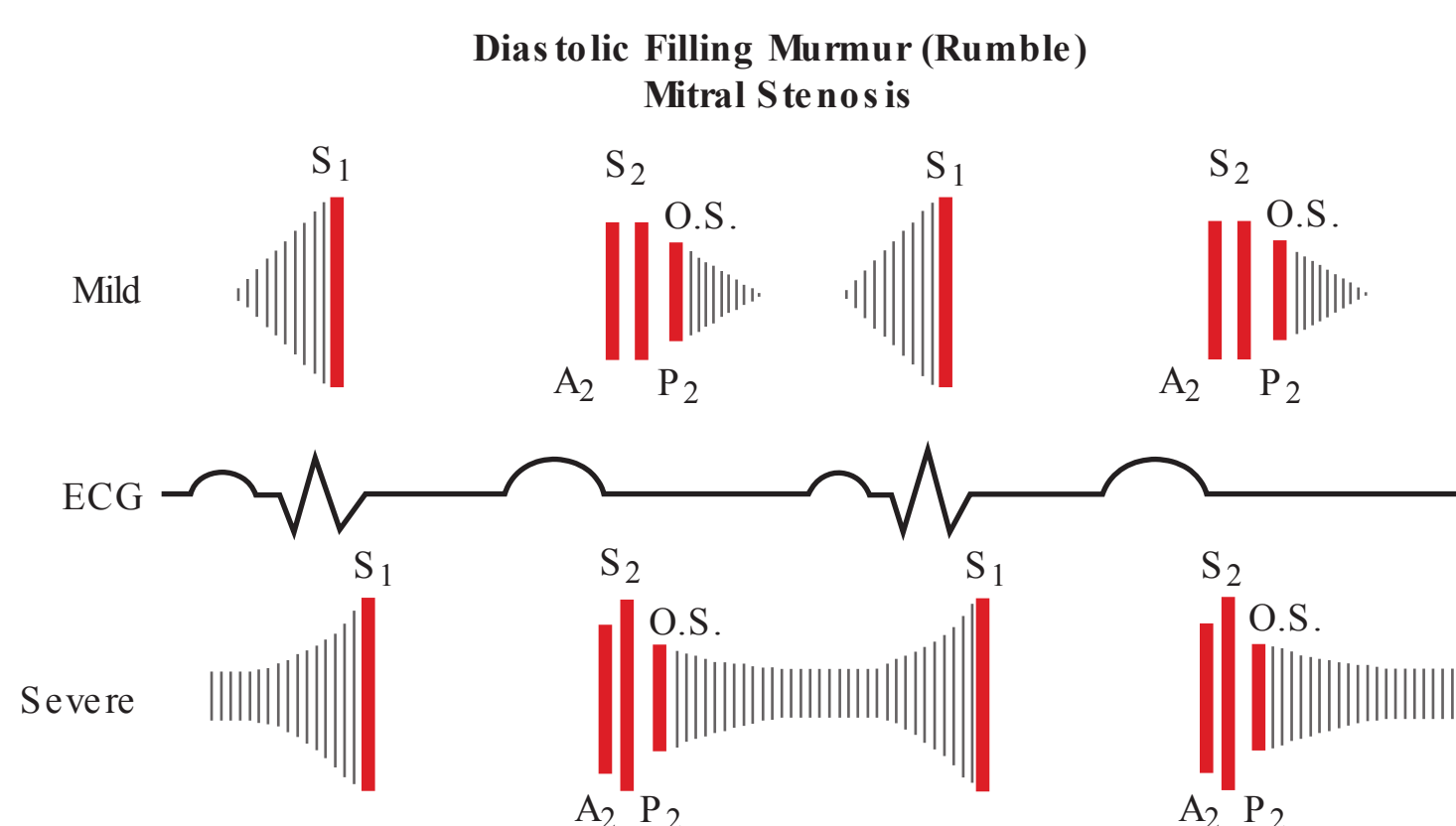


FIGURE 10-6

Diastolic filling murmur (rumble) in mitral stenosis. In mild mitral stenosis, the diastolic gradient across the valve is limited to the phases of rapid ventricular filling in early diastole and presystole. The rumble may occur during either or both periods. As the stenotic process becomes severe, a large pressure gradient exists across the valve during the entire diastolic filling period, and the rumble persists throughout diastole. As the left atrial pressure

becomes greater, the interval between A_2 (or P_2) and the opening snap (O.S.) shortens. In severe mitral stenosis, secondary pulmonary hypertension develops and results in a loud P_2 and the splitting interval usually narrows. ECG, electrocardiogram. (From JA Shaver, JJ Leonard, DF Leon: *Examination of the Heart, Part IV, Auscultation of the Heart*. Dallas, American Heart Association, 1990, p 55. Copyright, American Heart Association.)

including a wide pulse pressure, a “water-hammer” carotid upstroke (Corrigan’s pulse), and Quincke’s pulsations of the nail beds. The diastolic murmur of acute, severe AR is notably shorter in duration and lower pitched than the murmur of chronic AR. It can be very difficult to appreciate in the presence of a rapid heart rate. These attributes reflect the abrupt rate of rise of diastolic pressure within the unprepared and non-compliant left ventricle and the correspondingly rapid decline in the aortic–left ventricular diastolic pressure gradient. Left ventricular diastolic pressure may increase sufficiently to result in premature closure of the mitral valve and a soft first heart sound. Peripheral signs of significant diastolic run-off are not present.

Pulmonic regurgitation (PR) results in a decrescendo, early to mid-diastolic murmur (Graham Steell murmur) that begins after the pulmonic component of S_2 (P_2), is best heard at the second left interspace, and radiates along the left sternal border. The intensity of the murmur may increase with inspiration. PR is most commonly due to dilation of the valve annulus from chronic elevation of the pulmonary artery pressure. Signs of pulmonary hypertension, including a right ventricular lift and a loud, single or narrowly split S_2 , are present. These features also help distinguish PR from AR as the cause of a decrescendo diastolic murmur heard along the left sternal border. PR in the absence of pulmonary hypertension can occur with endocarditis or a congenitally deformed valve. It is usually present after repair of tetralogy of Fallot in childhood. When pulmonary hypertension is not present, the diastolic murmur is softer and lower pitched than the classic Graham Steell murmur, and the severity of the PR can be difficult to appreciate.

TTE is indicated for the further evaluation of a patient with an early to mid-diastolic murmur. Longitudinal assessment of the severity of the valve lesion and ventricular size and systolic function help guide a potential decision for surgical management. TTE also can provide anatomic information regarding the root and proximal ascending aorta, although computed tomographic or magnetic resonance angiography may be indicated for more precise characterization (**Chap. 12**).

Mid-diastolic murmurs

(**Figs. 10-1G and 10-1H**) Mid-diastolic murmurs result from obstruction and/or augmented flow at the level of the mitral or tricuspid valve. Rheumatic fever is the most common cause of MS (**Fig. 10-6**). In younger patients with pliable valves, S_1 is loud and the murmur begins after an opening snap, which is a high-pitched sound that occurs shortly after S_2 . The interval between the pulmonic component of the second heart sound (P_2) and the opening snap is inversely related to the

magnitude of the left atrial–left ventricular pressure gradient. The murmur of MS is low-pitched and thus is best heard with the bell of the stethoscope. It is loudest at the left ventricular apex and often is appreciated only when the patient is turned in the left lateral decubitus position. It is usually of grade 1 or 2 intensity but may be absent when the cardiac output is severely reduced despite significant obstruction. The intensity of the murmur increases during maneuvers that increase cardiac output and mitral valve flow, such as exercise. The duration of the murmur reflects the length of time over which left atrial pressure exceeds left ventricular diastolic pressure. An increase in the intensity of the murmur just before S_1 , a phenomenon known as presystolic accentuation (**Figs. 10-1A and 10-6**), occurs in patients in sinus rhythm and is due to a late increase in trans-mitral flow with atrial contraction. Presystolic accentuation does not occur in patients with atrial fibrillation.

The mid-diastolic murmur associated with tricuspid stenosis is best heard at the lower left sternal border and increases in intensity with inspiration. A prolonged y descent may be visible in the jugular venous waveform. This murmur is very difficult to hear and often is obscured by left-sided acoustical events.

There are several other causes of mid-diastolic murmurs. Large left atrial myxomas may prolapse across the mitral valve and cause variable degrees of obstruction to left ventricular inflow (**Chap. 29**). The murmur associated with an atrial myxoma may change in duration and intensity with changes in body position. An opening snap is not present, and there is no presystolic accentuation. Augmented mitral diastolic flow can occur with isolated severe MR or with a large left-to-right shunt at the ventricular or great vessel level and produce a soft, rapid filling sound (S_3) followed by a short, low-pitched mid-diastolic apical murmur. The Austin Flint murmur of severe, chronic AR has already been described.

A short, mid-diastolic murmur is rarely heard during an episode of acute rheumatic fever (Carey-Coombs murmur) and probably is due to flow through an edematous mitral valve. An opening snap is not present in the acute phase, and the murmur dissipates with resolution of the acute attack. Complete heart block with dys-synchronous atrial and ventricular activation may be associated with intermittent mid- to late diastolic murmurs if atrial contraction occurs when the mitral valve is partially closed. Mid-diastolic murmurs indicative of increased tricuspid valve flow can occur with severe, isolated TR and with large ASDs and significant left-to-right shunting. Other signs of an ASD are present (**Chap. 22**), including fixed splitting of S_2 and a mid-systolic murmur at the mid- to upper left sternal border. TTE is indicated for evaluation of a patient with a mid- to late diastolic murmur. Findings specific to the diseases discussed above will help guide management.

CONTINUOUS MURMURS

(Figs. 10-1H and 10-7) Continuous murmurs begin in systole, peak near the second heart sound, and continue into all or part of diastole. Their presence throughout the cardiac cycle implies a pressure gradient between two chambers or vessels during both systole and diastole. The continuous murmur associated with a patent ductus arteriosus is best heard at the upper left sternal border. Large, uncorrected shunts may lead to pulmonary hypertension, attenuation or obliteration of the diastolic component of the murmur, reversal of shunt flow, and differential cyanosis of the lower extremities. A ruptured sinus of Valsalva aneurysm creates a continuous murmur of abrupt onset at the upper right sternal border. Rupture typically occurs into a right heart chamber, and the murmur is indicative of a continuous pressure difference between the aorta and either the right ventricle or the right atrium. A continuous murmur also may be audible along the left sternal border with a coronary arteriovenous fistula and at the site of an arteriovenous fistula used for hemodialysis access. Enhanced flow through enlarged intercostal collateral arteries in patients with aortic coarctation may produce a continuous murmur along the course of one or more ribs. A cervical bruit with both systolic and diastolic components (a to-fro murmur, Fig. 10-7) usually indicates a high-grade carotid artery stenosis.

Not all continuous murmurs are pathologic. A continuous venous hum can be heard in healthy children

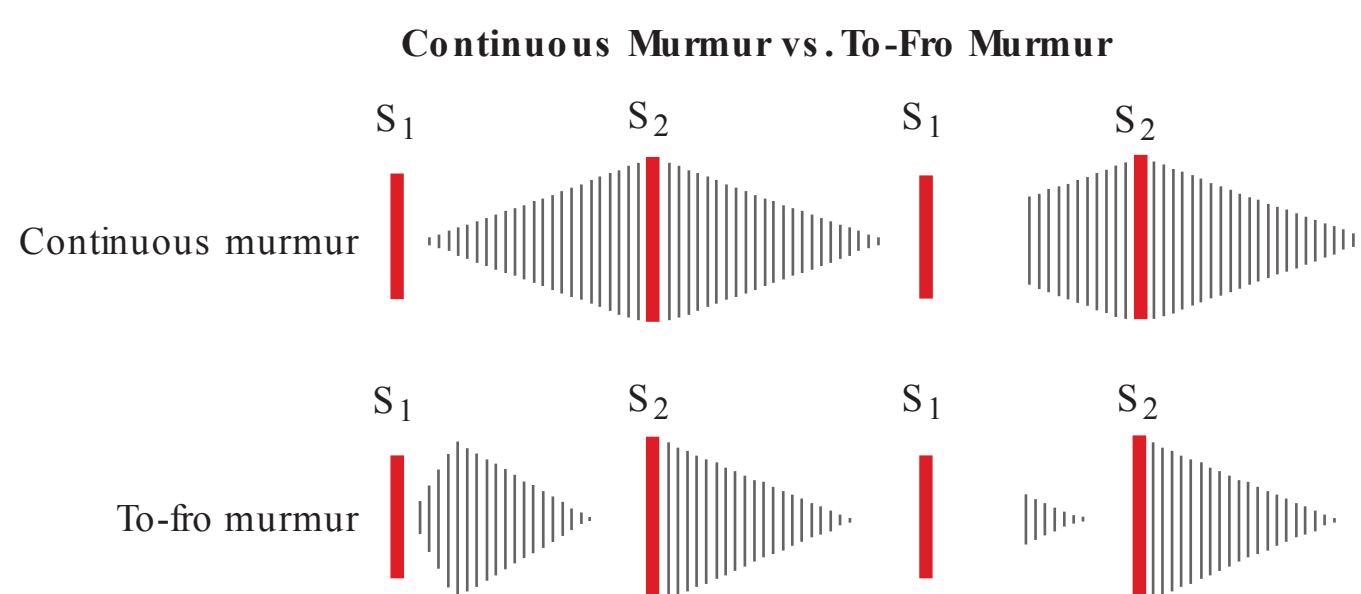


FIGURE 10-7

Comparison of the continuous murmur and the to-fro murmur. During abnormal communication between high-pressure and low-pressure systems, a large pressure gradient exists throughout the cardiac cycle, producing a continuous murmur. A classic example is patent ductus arteriosus. At times, this type of murmur can be confused with a to-fro murmur, which is a combination of systolic ejection murmur and a murmur of semilunar valve incompetence. A classic example of a to-fro murmur is aortic stenosis and regurgitation. A continuous murmur crescendos to near the second heart sound (S_2), whereas a to-fro murmur has two components. The mid-systolic ejection component decreases and disappears as it approaches S_2 . (From JA Shaver, JJ Leonard, DF Leon: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 55. Copyright, American Heart Association.)

and young adults, especially during pregnancy; it is best appreciated in the right supraclavicular fossa and can be obliterated by pressure over the right internal jugular vein or by having the patient turn his or her head toward the examiner. The continuous mammary soufflé of pregnancy is created by enhanced arterial flow through engorged breasts and usually appears during the late third trimester or early puerperium. The murmur is louder in systole. Firm pressure with the diaphragm of the stethoscope can eliminate the diastolic portion of the murmur.

DYNAMIC AUSCULTATION

(Table 10-2; see Table 9-1) Careful attention to the behavior of heart murmurs during simple maneuvers that alter cardiac hemodynamics can provide important clues to their cause and significance.

Respiration

Auscultation should be performed during quiet respiration or with a modest increase in inspiratory effort, as more forceful movement of the chest tends to obscure the heart sounds. Left-sided murmurs may be best heard at end expiration, when lung volumes are minimized and the heart and great vessels are brought closer to the chest wall. This phenomenon is characteristic of the murmur of AR. Murmurs of right-sided origin, such as tricuspid or pulmonic regurgitation, increase in intensity during inspiration. The intensity of left-sided murmurs either remains constant or decreases with inspiration.

Bedside assessment also should evaluate the behavior of S_2 with respiration and the dynamic relationship between the aortic and pulmonic components (Fig. 10-8). Reversed splitting can be a feature of severe AS, HOCM, left bundle branch block, right ventricular pacing, or acute myocardial ischemia. Fixed splitting of S_2 in the presence of a grade 2 or 3 mid-systolic murmur at the mid- or upper left sternal border indicates an ASD. Physiologic but wide splitting during the respiratory cycle implies either premature aortic valve closure,

TABLE 10-2

DYNAMIC AUSCULTATION: BEDSIDE MANEUVERS THAT CAN BE USED TO CHANGE THE INTENSITY OF CARDIAC MURMURS (SEE TEXT)

1. Respiration
2. Isometric exercise (handgrip)
3. Transient arterial occlusion
4. Pharmacologic manipulation of preload and/or afterload
5. Valsalva maneuver
6. Rapid standing/squatting
7. Passive leg raising
8. Post-premature beat

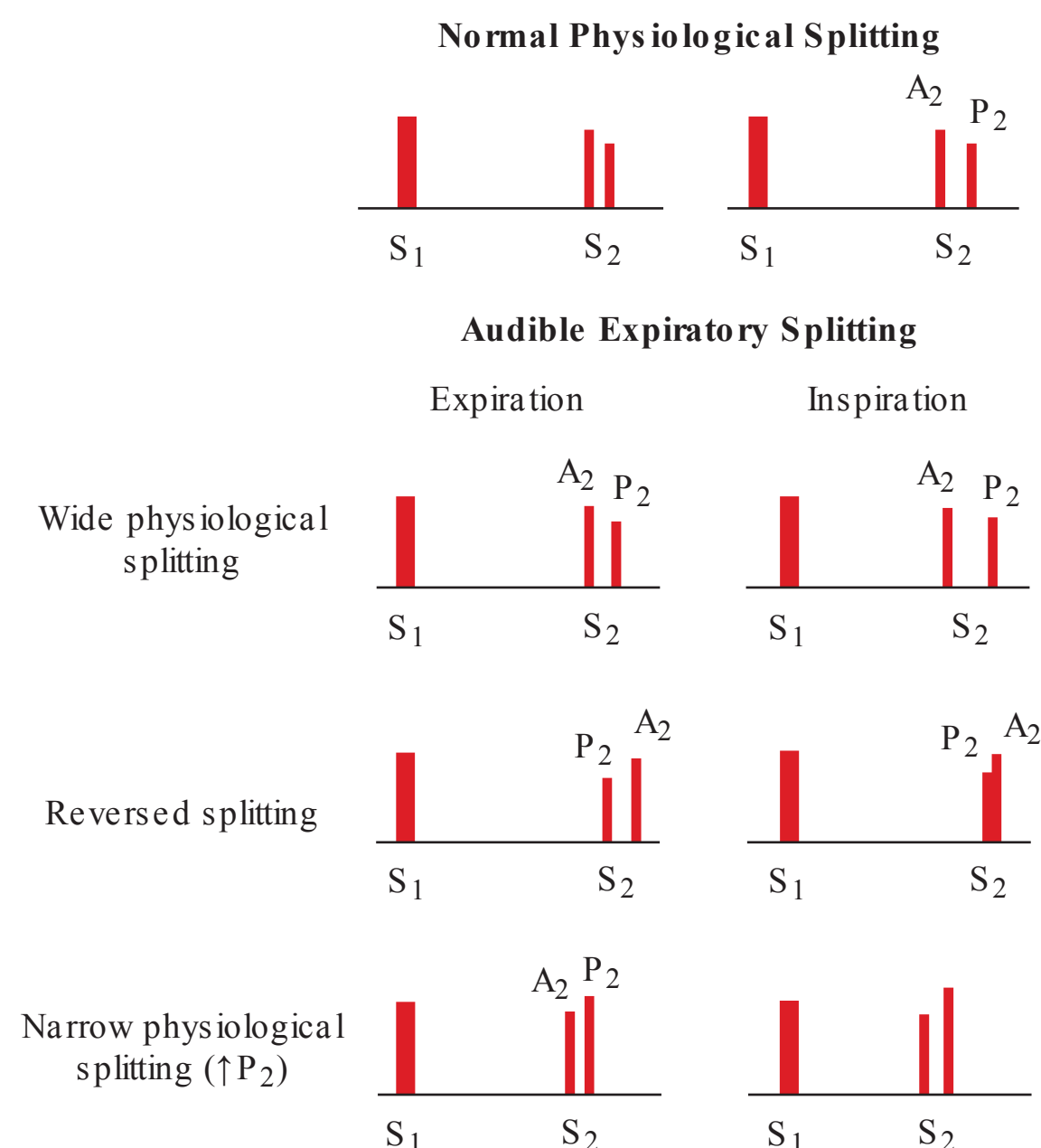


FIGURE 10-8

Top. Normal physiologic splitting. During expiration, the aortic (A_2) and pulmonic (P_2) components of the second heart sound are separated by <30 ms and are appreciated as a single sound. During inspiration, the splitting interval widens, and A_2 and P_2 are clearly separated into two distinct sounds. Bottom. Audible expiratory splitting. Wide physiologic splitting is caused by a delay in P_2 . Reversed splitting is caused by a delay in A_2 , resulting in paradoxical movement; i.e., with inspiration P_2 moves toward A_2 , and the splitting interval narrows. Narrow physiologic splitting occurs in pulmonary hypertension, and both A_2 and P_2 are heard during expiration at a narrow splitting interval because of the increased intensity and high-frequency composition of P_2 . (From JA Shaver, JJ Leonard, DF Leon: *Examination of the Heart, Part IV, Auscultation of the Heart*. Dallas, American Heart Association, 1990, p 17. Copyright, American Heart Association.)

as can occur with severe MR, or delayed pulmonic valve closure due to PS or right bundle branch block.

Alterations of systemic vascular resistance

Murmurs can change characteristics after maneuvers that alter systemic vascular resistance and left ventricular afterload. The systolic murmurs of MR and VSD become louder during sustained handgrip, simultaneous inflation of blood pressure cuffs on both upper extremities to pressures 20–40 mmHg above systolic pressure for 20 s, or infusion of a vasopressor agent. The murmurs associated with AS or HOCM will become softer or remain unchanged with these maneuvers. The diastolic murmur of AR becomes louder in response to interventions that raise systemic vascular resistance.

Opposite changes in systolic and diastolic murmurs may occur with the use of pharmacologic agents that

lower systemic vascular resistance. Inhaled amyl nitrite is now rarely used for this purpose but can help distinguish the murmur of AS or HOCM from that of either MR or VSD, if necessary. The former two murmurs increase in intensity, whereas the latter two become softer after exposure to amyl nitrite. As noted previously, the Austin Flint murmur of severe AR becomes softer, but the mid-diastolic rumble of MS becomes louder, in response to the abrupt lowering of systemic vascular resistance with amyl nitrite.

Changes in venous return

The Valsalva maneuver results in an increase in intrathoracic pressure, followed by a decrease in venous return, ventricular filling, and cardiac output. The majority of murmurs decrease in intensity during the strain phase of the maneuver. Two notable exceptions are the murmurs associated with MVP and obstructive HOCM, both of which become louder during the Valsalva maneuver. The murmur of MVP may also become longer as leaflet prolapse occurs earlier in systole at smaller ventricular volumes. These murmurs behave in a similar and parallel fashion with standing. Both the click and the murmur of MVP move closer in timing to S_1 on rapid standing from a squatting position (**Fig. 10-3**). The increase in the intensity of the murmur of HOCM is predicated on the augmentation of the dynamic left ventricular outflow tract gradient that occurs with reduced ventricular filling. Squatting results in abrupt increases in both venous return (preload) and left ventricular afterload that increase ventricular volume, changes that predictably cause a decrease in the intensity and duration of the murmurs associated with MVP and HOCM; the click and murmur of MVP move away from S_1 with squatting. Passive leg raising can be used to increase venous return in patients who are unable to squat and stand. This maneuver may lead to a decrease in the intensity of the murmur associated with HOCM but has less effect in patients with MVP.

Post-premature ventricular contraction

A change in the intensity of a systolic murmur in the first beat after a premature beat, or in the beat after a long cycle length in patients with atrial fibrillation, can help distinguish AS from MR, particularly in an older patient in whom the murmur of AS is well transmitted to the apex. Systolic murmurs due to left ventricular outflow obstruction, including that due to AS, increase in intensity in the beat after a premature beat because of the combined effects of enhanced left ventricular filling and post-extrasystolic potentiation of contractile function. Forward flow accelerates, causing an increase in the gradient and a louder murmur. The intensity of the murmur of MR does not change in the post-premature

beat as there is relatively little further increase in mitral valve flow or change in the left ventricular–left atrial gradient.

THE CLINICAL CONTEXT

Additional clues to the etiology and importance of a heart murmur can be gleaned from the history and other physical examination findings. Symptoms suggestive of cardiovascular, neurologic, or pulmonary disease help focus the differential diagnosis, as do findings relevant to the jugular venous pressure and waveforms, the arterial pulses, other heart sounds, the lungs, the abdomen, the skin, and the extremities. In many instances, laboratory studies, an ECG, and/or a chest x-ray may have been obtained earlier and may contain valuable information. A patient with suspected infective endocarditis, for example, may have a murmur in the setting of fever, chills, anorexia, fatigue, dyspnea, splenomegaly, petechiae, and positive blood cultures. A new systolic murmur in a patient with a marked fall in blood pressure after a recent MI suggests myocardial rupture. By contrast, an isolated grade 1 or 2 mid-systolic murmur at the left sternal border in a healthy, active, and asymptomatic young adult is most likely a benign finding for which no further evaluation is indicated. The context in which the murmur is appreciated often dictates the need for further testing.

ECHOCARDIOGRAPHY

(Fig. 10-9; Chaps. 9 and 12) Echocardiography with color flow and spectral Doppler is a valuable tool for the

assessment of cardiac murmurs. Information regarding valve structure and function, chamber size, wall thickness, ventricular function, estimated pulmonary artery pressures, intracardiac shunt flow, pulmonary and hepatic vein flow, and aortic flow can be ascertained readily. It is important to note that Doppler signals of trace or mild valvular regurgitation of no clinical consequence can be detected with structurally normal tricuspid, pulmonic, and mitral valves. Such signals are not likely to generate enough turbulence to create an audible murmur.

Echocardiography is indicated for the evaluation of patients with early, late, or holosystolic murmurs and patients with grade 3 or louder mid-systolic murmurs. Patients with grade 1 or 2 mid-systolic murmurs but other symptoms or signs of cardiovascular disease, including those from ECG or chest x-ray, should also undergo echocardiography. Echocardiography is also indicated for the evaluation of any patient with a diastolic murmur and for patients with continuous murmurs not due to a venous hum or mammary soufflé. Echocardiography also should be considered when there is a clinical need to verify normal cardiac structure and function in a patient whose symptoms and signs are probably noncardiac in origin. The performance of serial echocardiography to follow the course of asymptomatic individuals with valvular heart disease is a central feature of their longitudinal assessment and provides valuable information that may have an impact on decisions regarding the timing of surgery. Routine echocardiography is not recommended for asymptomatic patients with a grade 1 or 2 mid-systolic murmur without other signs of heart disease. For this category of

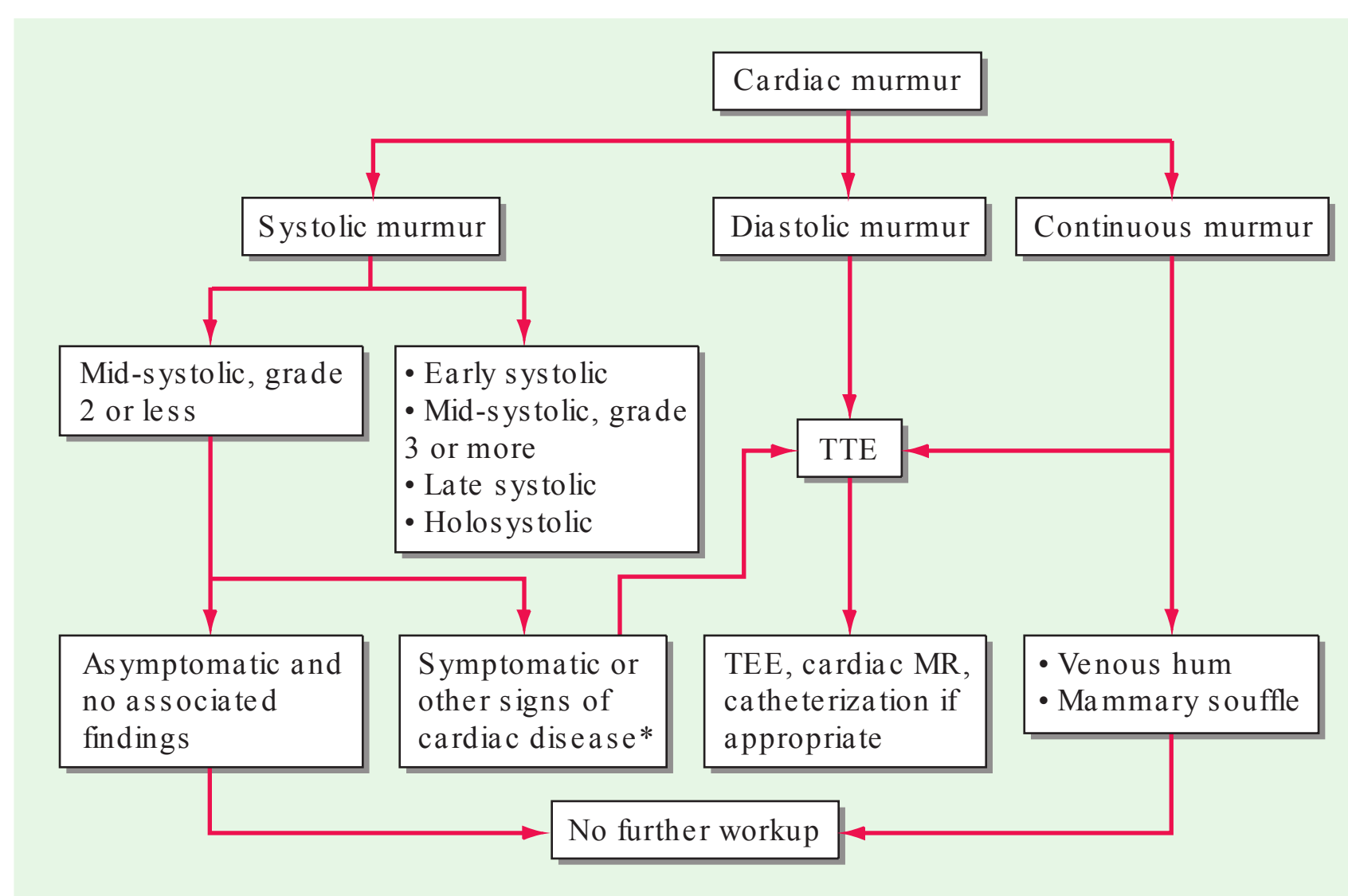


FIGURE 10-9

Strategy for evaluating heart murmurs. *If an electrocardiogram or chest x-ray has been obtained and is abnormal, echocardiography is indicated. TTE, transthoracic echocardiography; TEE,

transesophageal echocardiography; MR, magnetic resonance. (Adapted from RO Bonow et al: J Am Coll Cardiol 32:1486, 1998.)

patients, referral to a cardiovascular specialist should be considered if there is doubt about the significance of the murmur after the initial examination.

The selective use of echocardiography outlined above has not been subjected to rigorous analysis of its cost-effectiveness. For some clinicians, handheld or miniaturized cardiac ultrasound devices have replaced the stethoscope. Although several reports attest to the improved sensitivity of such devices for the detection of valvular heart disease, accuracy is highly operator-dependent, and incremental cost considerations and outcomes have not been addressed adequately. The use of electronic or digital stethoscopes with spectral display capabilities has also been proposed as a method to improve the characterization of heart murmurs and the mentored teaching of cardiac auscultation.

OTHER CARDIAC TESTING

(Chap. 12, Fig. 10-9) In relatively few patients, clinical assessment and TTE do not adequately characterize the origin and significance of a heart murmur. Transesophageal echocardiography (TEE) can be considered for further evaluation, especially when the TTE windows are limited by body size, chest configuration, or intrathoracic pathology. TEE offers enhanced sensitivity for the detection of a wide range of structural cardiac disorders. Electrocardiographically gated cardiac magnetic resonance (CMR) imaging, although limited in its ability to display valvular morphology, can provide quantitative information regarding valvular function, stenosis severity, regurgitant fraction, regurgitant volume, shunt flow, chamber and great vessel size,

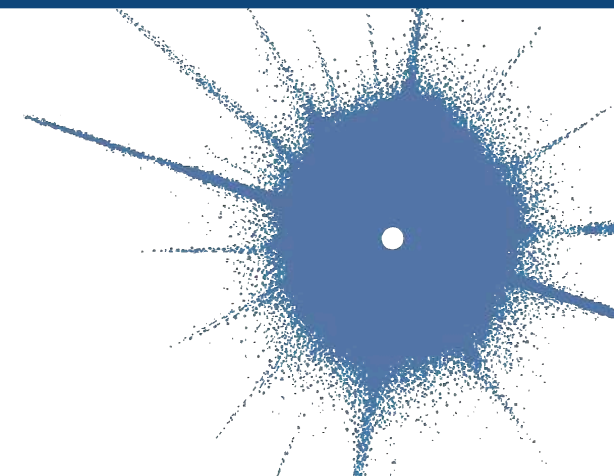
ventricular function, and myocardial perfusion. CMR has largely supplanted the need for cardiac catheterization and invasive hemodynamic assessment when there is a discrepancy between the clinical and echocardiographic findings. Invasive coronary angiography is performed routinely in most adult patients before valve surgery, especially when there is a suspicion of coronary artery disease predicated on symptoms, risk factors, and/or age. The use of computed tomography coronary angiography (CCTA) to exclude coronary artery disease in patients with a low pretest probability of disease before valve surgery is gaining wider acceptance.

INTEGRATED APPROACH

The accurate identification of a heart murmur begins with a systematic approach to cardiac auscultation. Characterization of its major attributes, as reviewed above, allows the examiner to construct a preliminary differential diagnosis, which is then refined by integration of information available from the history, associated cardiac findings, the general physical examination, and the clinical context. The need for and urgency of further testing follow sequentially. Correlation of the findings on auscultation with the noninvasive data provides an educational feedback loop and an opportunity for improving physical examination skills. Cost constraints mandate that noninvasive imaging be justified on the basis of its incremental contribution to diagnosis, treatment, and outcome. Additional study is required to assess the cost-effective application of newer imaging technology in patients with heart murmurs.

CHAPTER 11

ELECTROCARDIOGRAPHY



Ary L. Goldberger

An electrocardiogram (ECG or EKG) is a graphic recording of electric potentials generated by the heart. The signals are detected by means of metal electrodes attached to the extremities and chest wall and then are amplified and recorded by the electrocardiograph. ECG leads actually display the instantaneous differences in potential between the electrodes.

The clinical utility of the ECG derives from its immediate availability as a noninvasive, inexpensive, and highly versatile test. In addition to its use in detecting arrhythmias, conduction disturbances, and myocardial ischemia, electrocardiography may reveal findings related to life-threatening metabolic disturbances (e.g., hyperkalemia) or increased susceptibility to sudden cardiac death (e.g., QT prolongation syndromes).

ELECTROPHYSIOLOGY

(See also Chaps. 15 and 17) Depolarization of the heart is the initiating event for cardiac contraction. The electric currents that spread through the heart are produced by three components: cardiac pacemaker cells, specialized conduction tissue, and the heart muscle itself. The ECG, however, records only the depolarization (stimulation) and repolarization (recovery) potentials generated by the “working” atrial and ventricular myocardium.

The depolarization stimulus for the normal heartbeat originates in the sinoatrial (SA) node (Fig. 11-1), or sinus node, a collection of pacemaker cells. These cells fire spontaneously; that is, they exhibit automaticity. The first phase of cardiac electrical activation is the spread of the depolarization wave through the right and left atria, followed by atrial contraction. Next, the impulse stimulates pacemaker and specialized conduction tissues in the atrioventricular (AV) nodal and His-bundle areas; together, these two regions constitute the AV junction. The bundle of His bifurcates into two main branches, the right and left bundles, which rapidly

transmit depolarization wavefronts to the right and left ventricular myocardium by way of Purkinje fibers. The main left bundle bifurcates into two primary subdivisions: a left anterior fascicle and a left posterior fascicle. The depolarization wavefronts then spread through the ventricular wall, from endocardium to epicardium, triggering ventricular contraction.

Since the cardiac depolarization and repolarization waves have direction and magnitude, they can be represented by vectors. Vector analysis illustrates a central concept of electrocardiography: The ECG records the complex spatial and temporal summation of electrical potentials from multiple myocardial fibers conducted to the surface of the body. This principle accounts for inherent limitations in both ECG sensitivity (activity from certain cardiac regions may be canceled out or may be too weak to be recorded) and specificity (the same vectorial sum can result from either a selective gain or a loss of forces in opposite directions).

ECG WAVEFORMS AND INTERVALS

The ECG waveforms are labeled alphabetically, beginning with the P wave, which represents atrial depolarization (Fig. 11-2). The QRS complex represents ventricular depolarization, and the ST-T-U complex (ST segment, T wave, and U wave) represents ventricular repolarization. The J point is the junction between the end of the QRS complex and the beginning of the ST segment. Atrial repolarization (ST_a and T_a) is usually too low in amplitude to be detected, but it may become apparent in conditions such as acute pericarditis and atrial infarction.

The QRS-T waveforms of the surface ECG correspond in a general way with the different phases of simultaneously obtained ventricular action potentials, the intracellular recordings from single myocardial fibers (Chap. 15). The rapid upstroke (phase 0) of the action potential corresponds to the onset of QRS. The

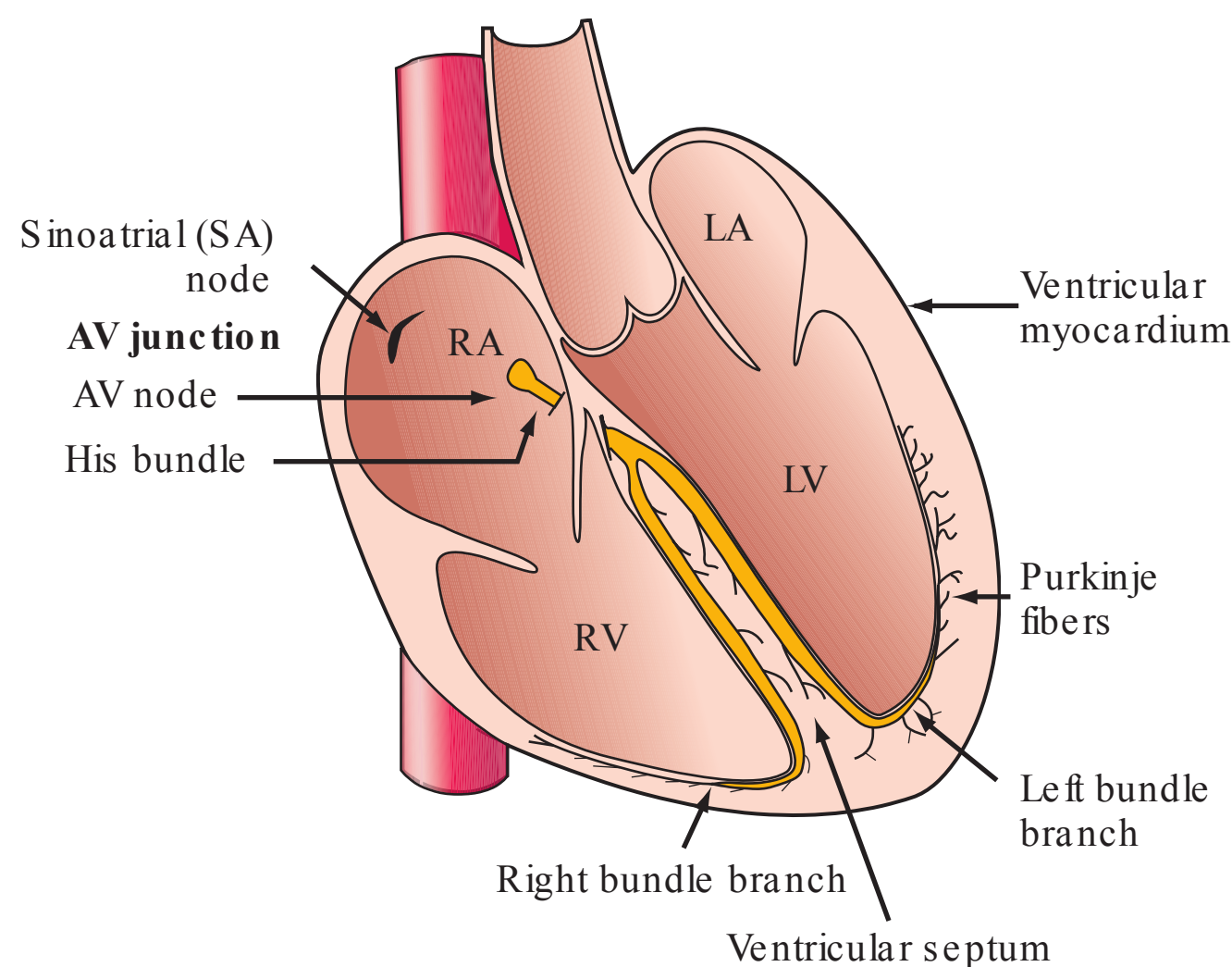


FIGURE 11-1

Schematic of the cardiac conduction system.

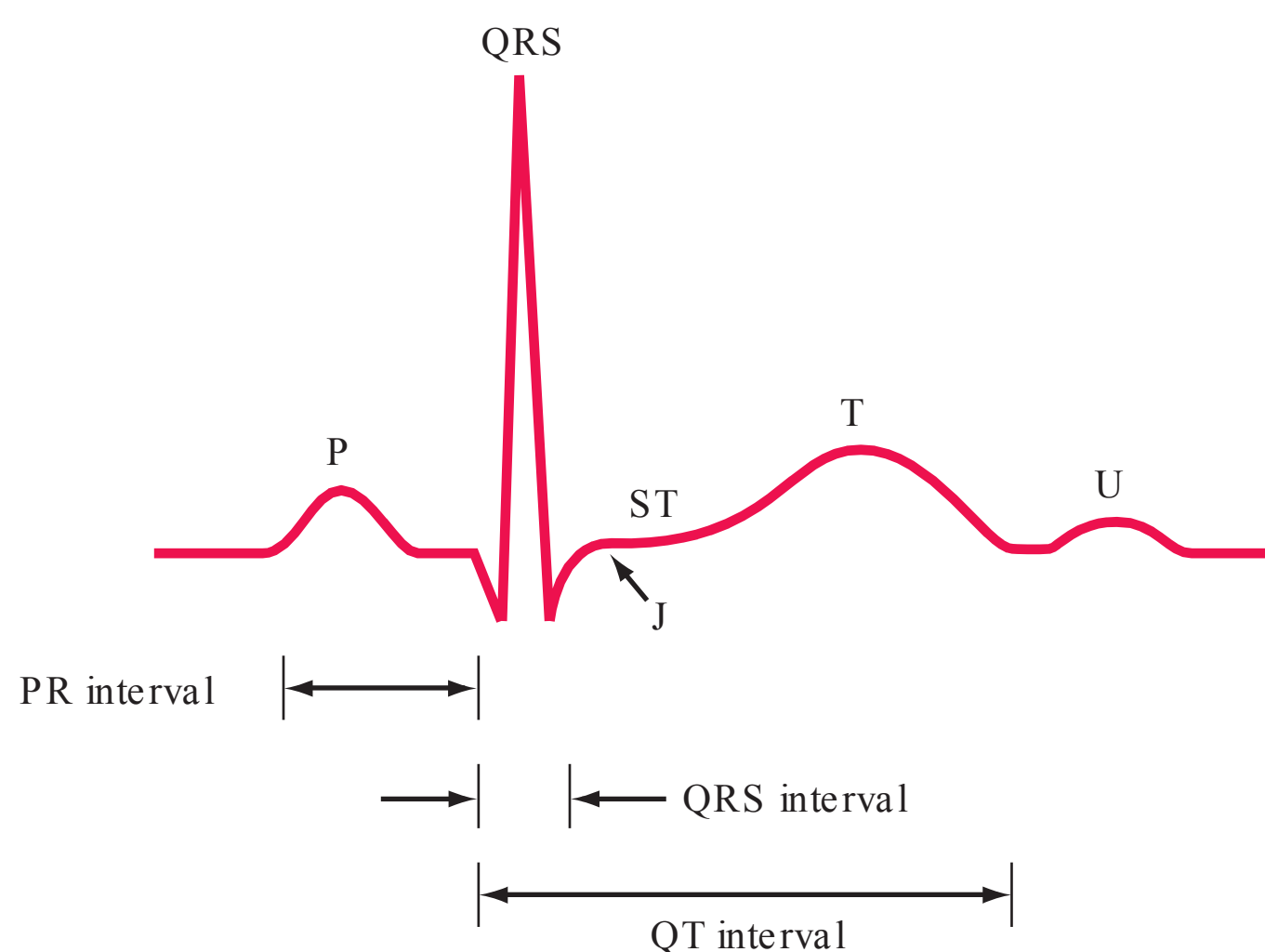


FIGURE 11-2

Basic ECG waveforms and intervals. Not shown is the RR interval, the time between consecutive QRS complexes.

plateau (phase 2) corresponds to the isoelectric ST segment, and active repolarization (phase 3) corresponds to the inscription of the T wave. Factors that decrease the slope of phase 0 by impairing the influx of Na^+ (e.g., hyperkalemia and drugs such as flecainide) tend to increase QRS duration. Conditions that prolong phase 2 (amiodarone, hypocalcemia) increase the QT interval. In contrast, shortening of ventricular repolarization (phase 2), such as by digitalis administration or hypercalcemia, abbreviates the ST segment.

The ECG ordinarily is recorded on special graph paper that is divided into 1-mm² gridlike boxes. Since the usual ECG paper speed is 25 mm/s, the

smallest (1 mm) horizontal divisions correspond to 0.04 (40 ms), with heavier lines at intervals of 0.20 s (200 ms). Vertically, the ECG graph measures the amplitude of a specific wave or deflection (1 mV = 10 mm with standard calibration; the voltage criteria for hypertrophy mentioned below are given in millimeters). There are four major ECG intervals: RR, PR, QRS, and QT (Fig. 11-2). The heart rate (beats per minute) can be computed readily from the interbeat (RR) interval by dividing the number of large (0.20 s) time units between consecutive R waves into 300 or the number of small (0.04 s) units into 1500. The PR interval measures the time (normally 120–200 ms) between atrial and ventricular depolarization, which includes the physiologic delay imposed by stimulation of cells in the AV junction area. The QRS interval (normally 100–110 ms or less) reflects the duration of ventricular depolarization. The QT interval includes both ventricular depolarization and repolarization times and varies inversely with the heart rate. A rate-related (“corrected”) QT interval, QT_c , can be calculated as $\text{QT}/\sqrt{\text{RR}}$ and normally is ≤ 0.44 s. (Some references give QT_c upper normal limits as 0.43 s in men and 0.45 s in women. Also, a number of different formulas have been proposed, without consensus, for calculating the QT_c .)

The QRS complex is subdivided into specific deflections or waves. If the initial QRS deflection in a particular lead is negative, it is termed a Q wave; the first positive deflection is termed an R wave. A negative deflection after an R wave is an S wave. Subsequent positive or negative waves are labeled R' and S', respectively. Lowercase letters (qrs) are used for waves of relatively small amplitude. An entirely negative QRS complex is termed a QS wave.

ECG LEADS

The 12 conventional ECG leads record the difference in potential between electrodes placed on the surface of the body. These leads are divided into two groups: six limb (extremity) leads and six chest (precordial) leads. The limb leads record potentials transmitted onto the frontal plane (Fig. 11-3A), and the chest leads record potentials transmitted onto the horizontal plane (Fig. 11-3B).

The spatial orientation and polarity of the six frontal plane leads is represented on the hexaxial diagram (Fig. 11-4). The six chest leads (Fig. 11-5) are unipolar recordings obtained by electrodes in the following positions: lead V₁, fourth intercostal space, just to the right of the sternum; lead V₂, fourth intercostal space, just to the left of the sternum; lead V₃, midway between V₂ and V₄; lead V₄, midclavicular line, fifth intercostal space; lead V₅, anterior axillary line, same level as V₄; and lead V₆, midaxillary line, same level as V₄ and V₅. Additional

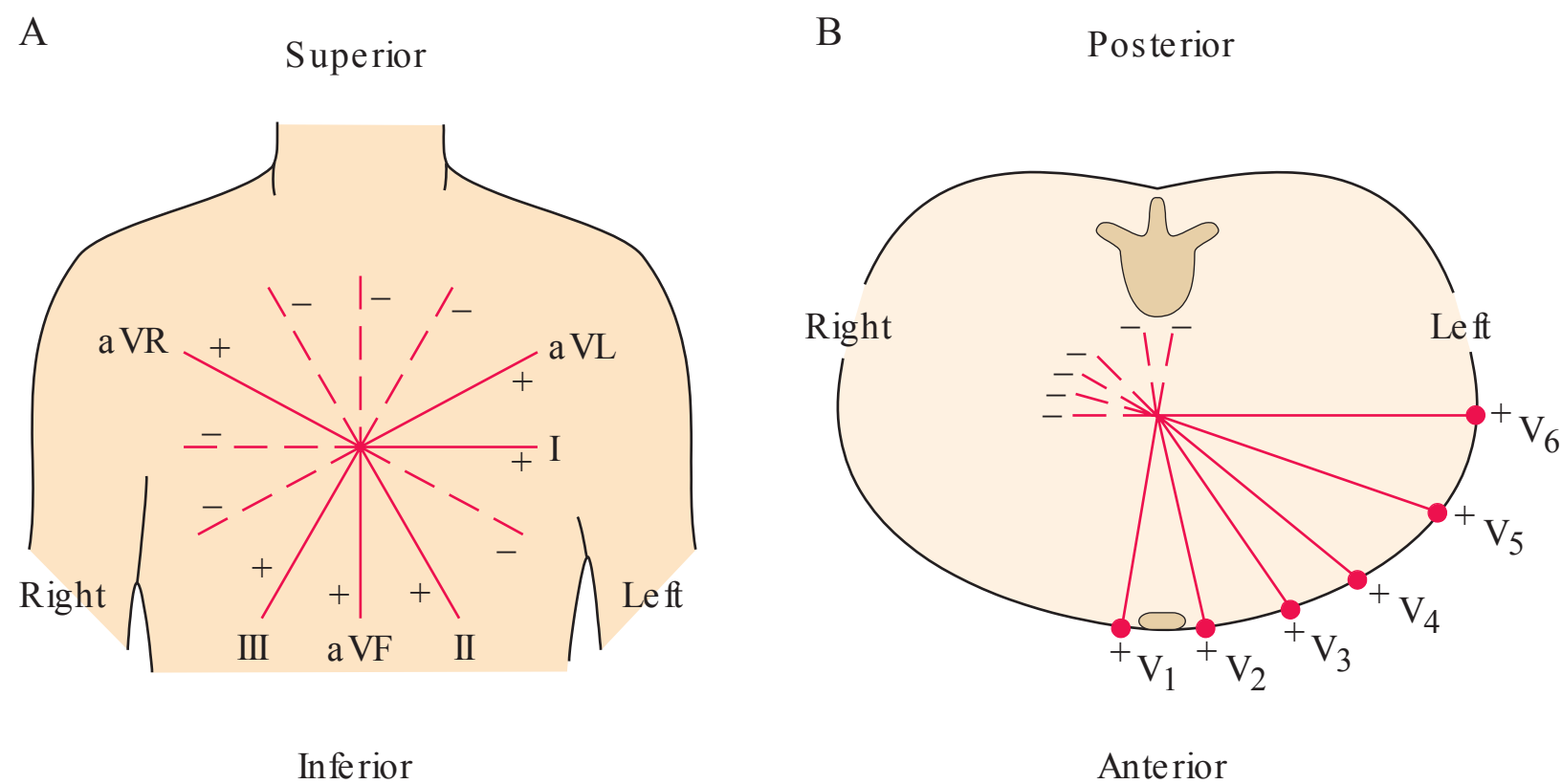


FIGURE 11-3

The six frontal plane (A) and six horizontal plane (B) leads provide a three-dimensional representation of cardiac electrical activity.

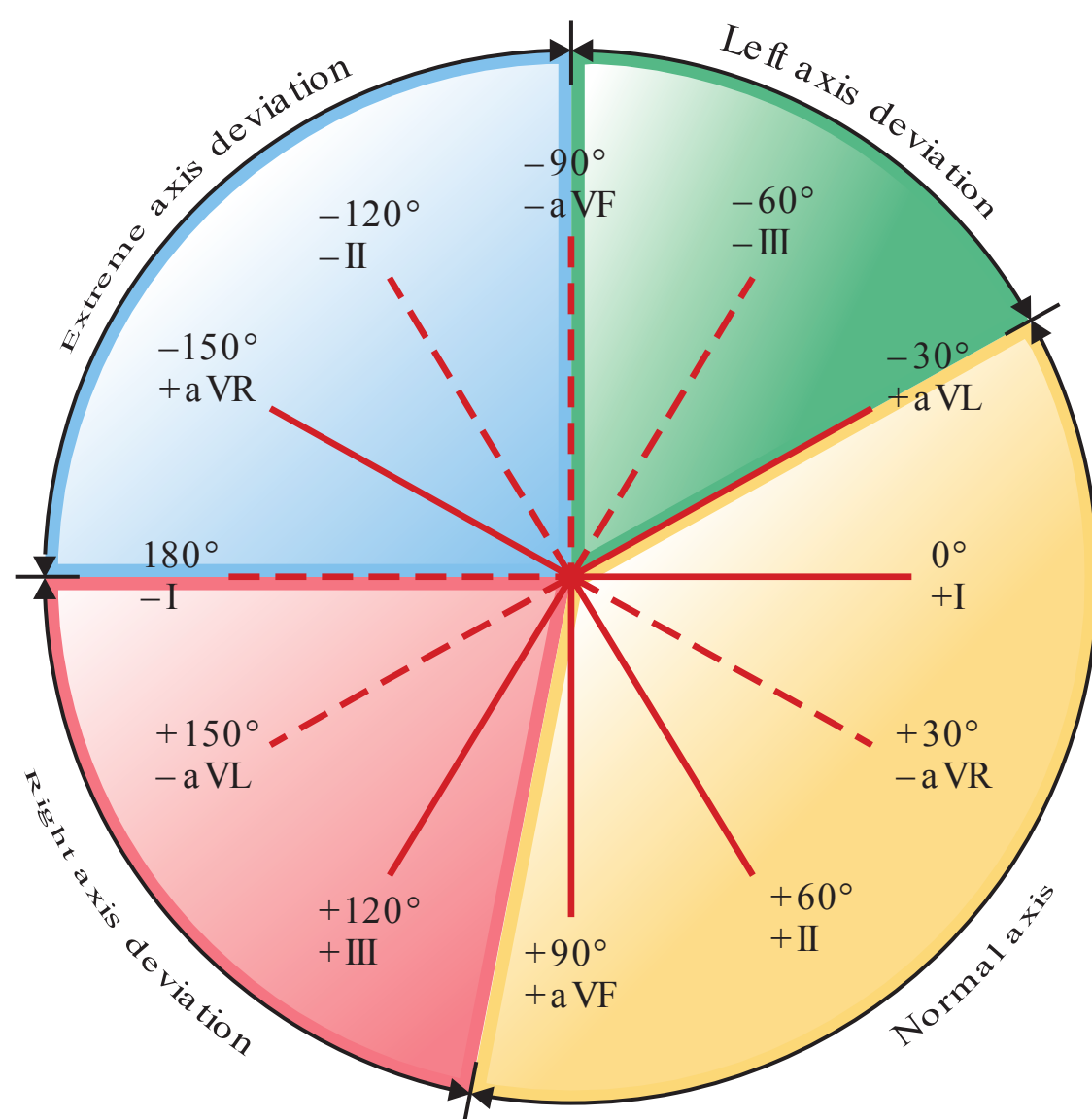


FIGURE 11-4

The frontal plane (limb or extremity) leads are represented on a hexaxial diagram. Each ECG lead has a specific spatial orientation and polarity. The positive pole of each lead axis (solid line) and the negative pole (hatched line) are designated by their angular position relative to the positive pole of lead I (0°). The mean electrical axis of the QRS complex is measured with respect to this display.

posterior leads are sometimes placed on the same horizontal plane as V₄ to facilitate detection of acute posterolateral infarction (V₇, midaxillary line; V₈ posterior axillary line; and V₉, posterior scapular line).

Together, the frontal and horizontal plane electrodes provide a three-dimensional representation of cardiac electrical activity. Each lead can be likened to a different video camera angle “looking” at the same events—atrial and ventricular depolarization and repolarization—from different spatial orientations. The conventional 12-lead ECG can be supplemented with additional leads in special circumstances. For example, right precordial leads V_{3R}, V_{4R}, etc., are useful in detecting evidence of

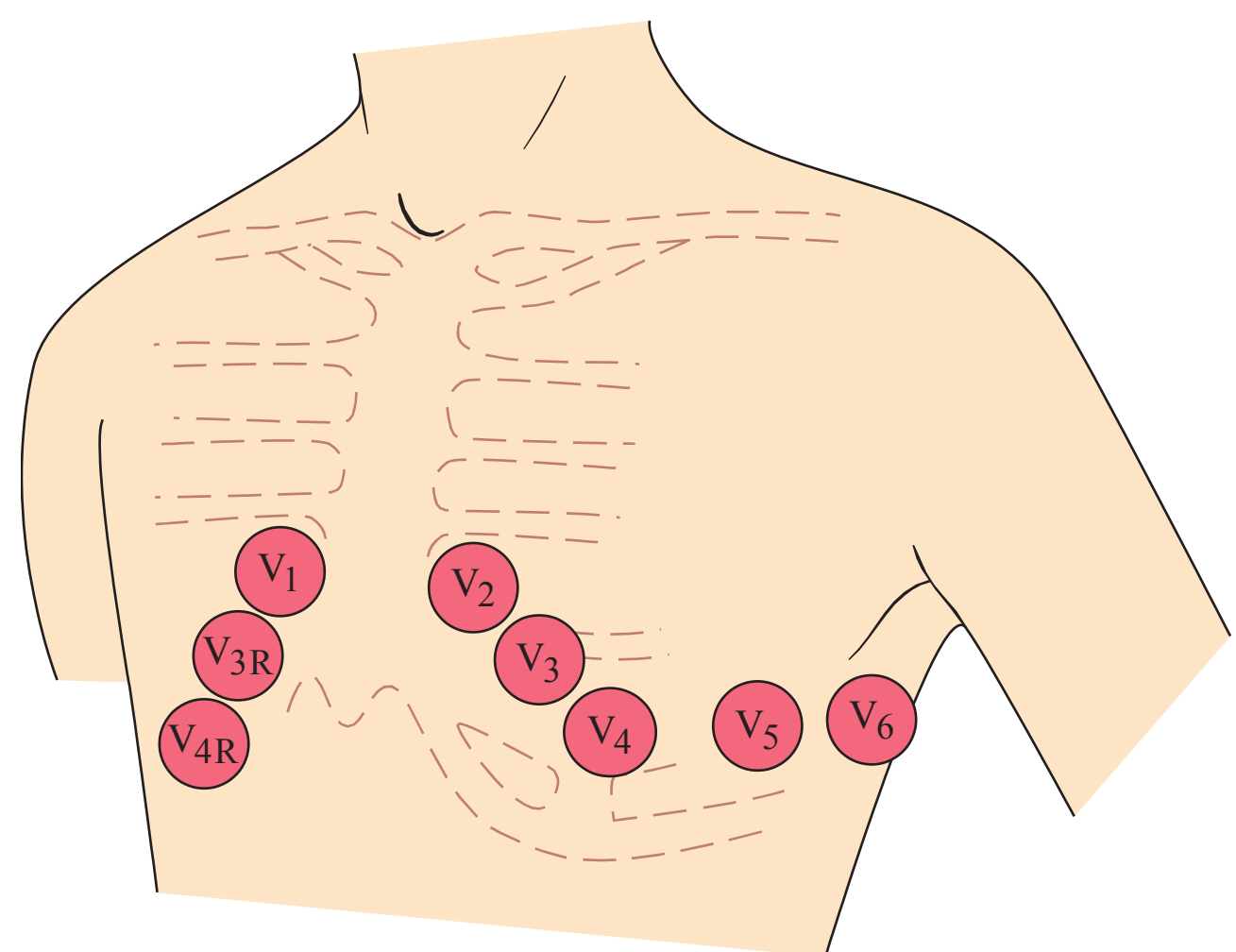


FIGURE 11-5

The horizontal plane (chest or precordial) leads are obtained with electrodes in the locations shown.

acute right ventricular ischemia. Bedside monitors and ambulatory ECG (Holter) recordings usually employ only one or two modified leads. **Intracardiac electrocardiography and electrophysiologic testing are discussed in Chaps. 15 and 17.**

The ECG leads are configured so that a positive (upright) deflection is recorded in a lead if a wave of depolarization spreads toward the positive pole of that lead, and a negative deflection is recorded if the wave spreads toward the negative pole. If the mean orientation of the depolarization vector is at right angles to a particular lead axis, a biphasic (equally positive and negative) deflection will be recorded.

GENESIS OF THE NORMAL ECG

P WAVE

The normal atrial depolarization vector is oriented downward and toward the subject's left, reflecting

the spread of depolarization from the sinus node to the right and then the left atrial myocardium. Since this vector points toward the positive pole of lead II and toward the negative pole of lead aVR, the normal P wave will be positive in lead II and negative in lead aVR. By contrast, activation of the atria from an ectopic pacemaker in the lower part of either atrium or in the AV junction region may produce retrograde P waves (negative in lead II, positive in lead aVR). The normal P wave in lead V₁ may be biphasic with a positive component reflecting right atrial depolarization, followed by a small (<1 mm²) negative component reflecting left atrial depolarization.

QRS COMPLEX

Normal ventricular depolarization proceeds as a rapid, continuous spread of activation wave fronts. This complex process can be divided into two major sequential phases, and each phase can be represented by a mean vector (Fig. 11-6). The first phase is depolarization of the interventricular septum from the left to the right and anteriorly (vector 1). The second results from the simultaneous depolarization of the right and left ventricles; it normally is dominated by the more massive left ventricle, so that vector 2 points leftward and posteriorly. Therefore, a right precordial lead (V₁) will record this biphasic depolarization process with a small positive deflection (septal r wave) followed by a larger negative deflection (S wave). A left precordial lead, e.g., V₆, will record the same sequence with a small negative deflection (septal q wave) followed by a relatively tall positive deflection (R wave). Intermediate leads show a relative increase in R-wave amplitude (normal R-wave progression) and a decrease in S-wave amplitude progressing across the chest from right to left. The precordial lead where the R and S waves are of approximately

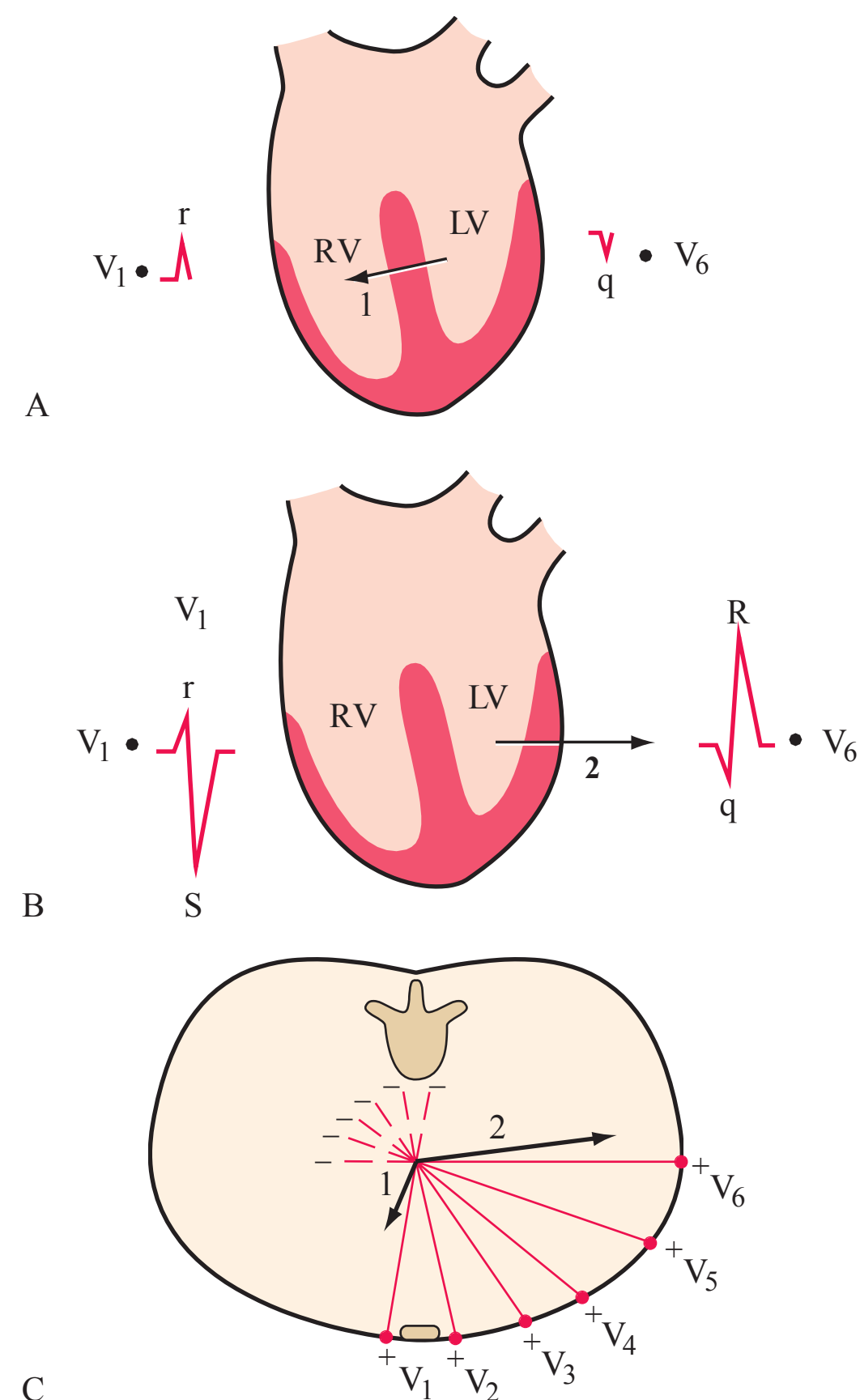


FIGURE 11-6

Ventricular depolarization can be divided into two major phases, each represented by a vector. A. The first phase (arrow 1) denotes depolarization of the ventricular septum, beginning on the left side and spreading to the right. This process is represented by a small “septal” r wave in lead V₁ and a small septal q wave in lead V₆. B. Simultaneous depolarization of the left and right ventricles (LV and RV) constitutes the second phase. Vector 2 is oriented to the left and posteriorly, reflecting the electrical predominance of the LV. C. Vectors (arrows) representing these two phases are shown in reference to the horizontal plane leads. (After ALGoldberger et al: Goldberger’s Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.)

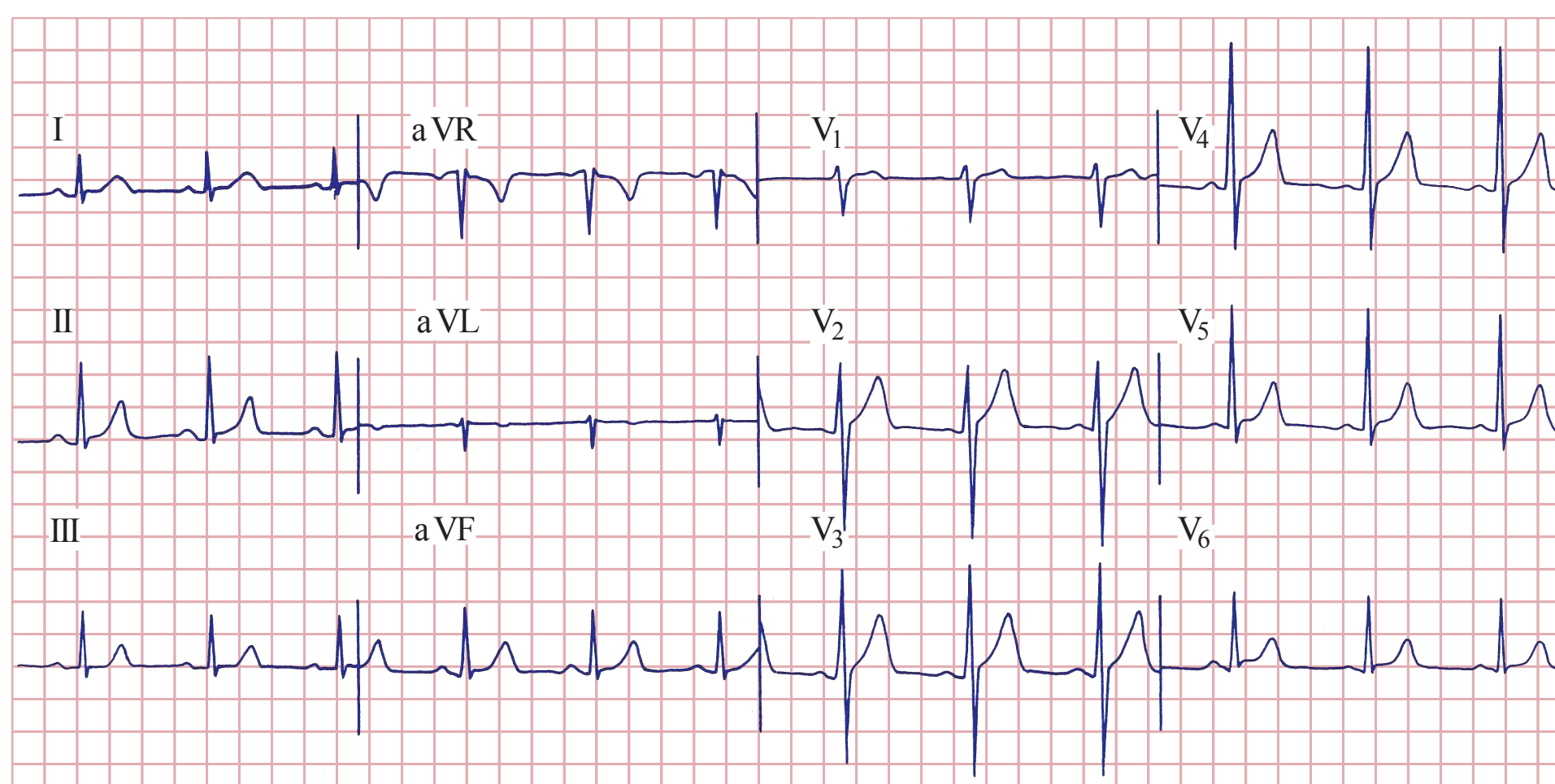


FIGURE 11-7

Normal electrocardiogram from a healthy subject. Sinus rhythm is present with a heart rate of 75 beats per minute. PR interval is 0.16 s; QRS interval (duration) is 0.08 s; QT interval is 0.36 s; QT_c is 0.40 s; the mean QRS axis is about +70°. The precordial leads show normal R-wave progression with the transition zone (R wave = S wave) in lead V₃.

96 equal amplitude is referred to as the transition zone (usually V_3 or V_4) (Fig. 11-7).

The QRS pattern in the extremity leads may vary considerably from one normal subject to another depending on the electrical axis of the QRS, which describes the mean orientation of the QRS vector with reference to the six frontal plane leads. Normally, the QRS axis ranges from -30° to $+100^\circ$ (Fig. 11-4). An axis more negative than -30° is referred to as left axis deviation, and an axis more positive than $+100^\circ$ is referred to as right axis deviation. Left axis deviation may occur as a normal variant but is more commonly associated with left ventricular hypertrophy, a block in the anterior fascicle of the left bundle system (left anterior fascicular block or hemiblock), or inferior myocardial infarction. Right axis deviation also may occur as a normal variant (particularly in children and young adults), as a spurious finding due to reversal of the left and right arm electrodes, or in conditions such as right ventricular overload (acute or chronic), infarction of the lateral wall of the left ventricle, dextrocardia, left pneumothorax, and left posterior fascicular block.

T WAVE AND U WAVE

Normally, the mean T-wave vector is oriented roughly concordant with the mean QRS vector (within about 45° in the frontal plane). Since depolarization and repolarization are electrically opposite processes, this normal QRS–T-wave vector concordance indicates that repolarization normally must proceed in the reverse direction from depolarization (i.e., from ventricular epicardium to endocardium). The normal U wave is a small, rounded deflection (≤ 1 mm) that follows the T wave and usually has the same polarity as the T wave. An abnormal increase in U-wave amplitude is most commonly due to drugs (e.g., dofetilide, amiodarone, sotalol, quinidine) or to hypokalemia. Very prominent U waves are a marker of increased susceptibility to the torsades de pointes type of ventricular tachycardia (Chap. 17). Inversion of the U wave in the precordial leads is abnormal and may be a subtle sign of ischemia.

MAJOR ECG ABNORMALITIES

CARDIAC ENLARGEMENT AND HYPERTROPHY

Right atrial overload (acute or chronic) may lead to an increase in P-wave amplitude (≥ 2.5 mm) (Fig. 11-8), sometimes referred to as “P-pulmonale.” Left atrial overload typically produces a biphasic P wave in V_1 with a broad negative component or a broad (≥ 120 ms), often notched P wave in one or more limb leads

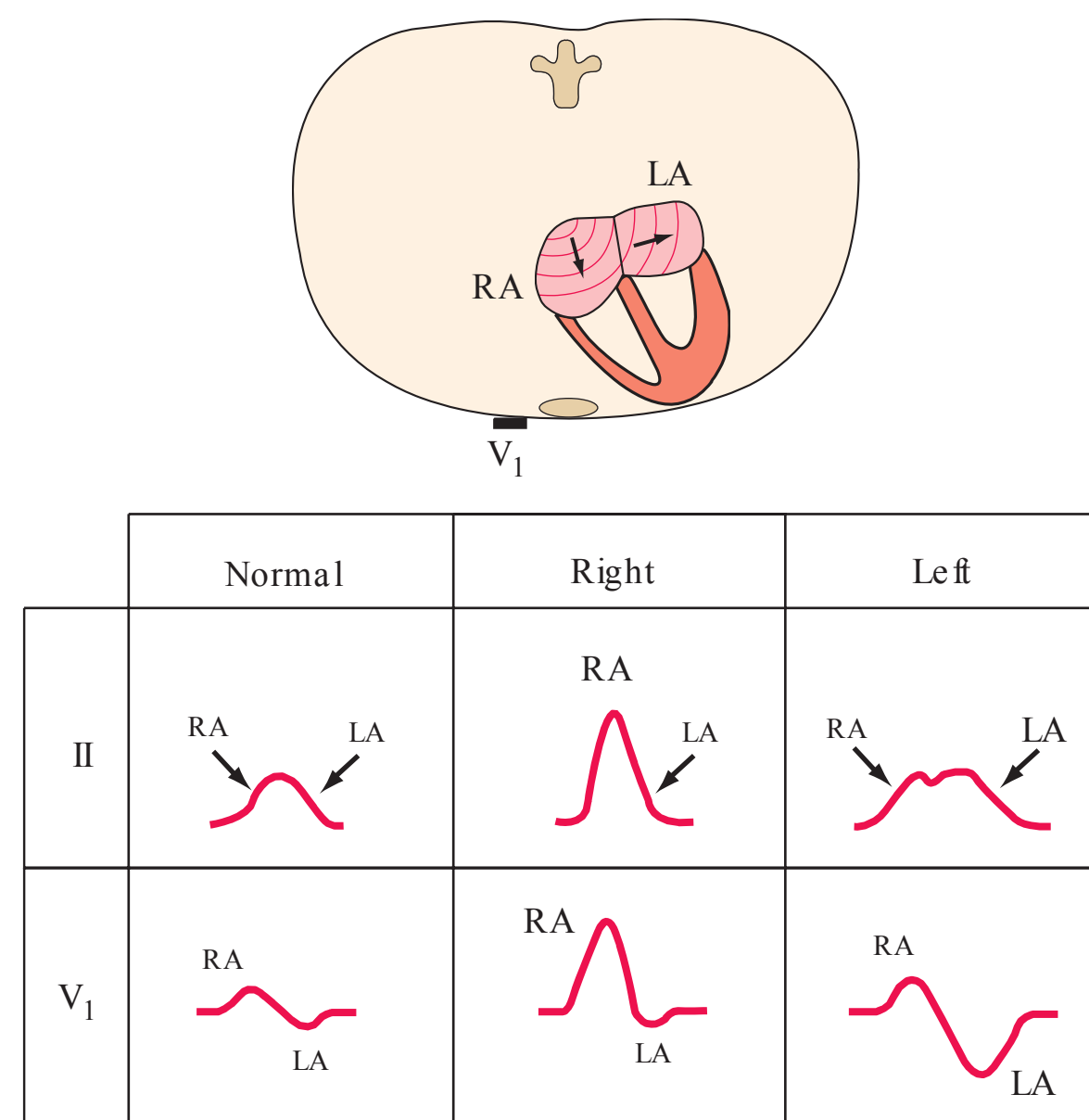


FIGURE 11-8

Right atrial (RA) overload may cause tall, peaked P waves in the limb or precordial leads. Left atrial (LA) abnormality may cause broad, often notched P waves in the limb leads and a biphasic P wave in lead V_1 with a prominent negative component representing delayed depolarization of the LA. (After MKPark, WG Guntheroth: How to Read Pediatric ECGs, 4th ed. St. Louis, Mosby/Elsevier, 2006.)

(Fig. 11-8). T is pattern, previously referred to as “P-mitrale,” may also occur with left atrial conduction delays in the absence of actual atrial enlargement, leading to the more general designation of left atrial abnormality.

Right ventricular hypertrophy due to a sustained, severe pressure load (e.g., due to tight pulmonic valve stenosis or certain pulmonary artery hypertension syndromes) is characterized by a relatively tall R wave in lead V_1 ($R \geq S$ wave), usually with right axis deviation (Fig. 11-9); alternatively, there may be a qR pattern in V_1 or V_3R . ST depression and T-wave inversion in the right-to-midprecordial leads are also often present. T is pattern, formerly called right ventricular “strain,” is attributed to repolarization abnormalities in acutely or chronically overloaded muscle. Prominent S waves may occur in the left lateral precordial leads. Right ventricular hypertrophy due to ostium secundum–type atrial septal defects, with the accompanying right ventricular volume overload, is commonly associated with an incomplete or complete right bundle branch block pattern with a rightward QRS axis.

Acute cor pulmonale due to pulmonary embolism (Chap. 45), for example, may be associated with a normal ECG or a variety of abnormalities. Sinus tachycardia is the most common arrhythmia, although other tachyarrhythmias, such as atrial fibrillation or flutter,

may occur. The QRS axis may shift to the right, sometimes in concert with the so-called $S_1Q_3T_3$ pattern (prominence of the S wave in lead I and the Q wave in lead III, with T-wave inversion in lead III). Acute right ventricular dilation also may be associated with slow R-wave progression and ST-T abnormalities in V_1 to V_4 simulating acute anterior infarction. A right ventricular conduction disturbance may appear.

Chronic cor pulmonale due to obstructive lung disease (**Chap. 19**) usually does not produce the classic ECG patterns of right ventricular hypertrophy noted above. Instead of tall right precordial R waves, chronic lung disease more typically is associated with small R waves in right-to-midprecordial leads (slow R-wave progression) due in part to downward displacement of the diaphragm and the heart. Low-voltage complexes are commonly present, owing to hyperaeration of the lungs.

A number of different voltage criteria for left ventricular hypertrophy (Fig. 11-9) have been proposed on the basis of the presence of tall left precordial R waves and deep right precordial S waves (e.g., $SV_1 + [RV_5 \text{ or } RV_6] > 35 \text{ mm}$). Repolarization abnormalities (ST depression

with T-wave inversions, formerly called the left ventricular “strain” pattern) also may appear in leads with prominent R waves. However, prominent precordial voltages may occur as a normal variant, especially in athletic or young individuals. Left ventricular hypertrophy may increase limb lead voltage with or without increased precordial voltage (e.g., $RaVL + SV_3 > 20 \text{ mm}$ in women and $>28 \text{ mm}$ in men). The presence of left atrial abnormality increases the likelihood of underlying left ventricular hypertrophy in cases with borderline voltage criteria. Left ventricular hypertrophy often progresses to incomplete or complete left bundle branch block. The sensitivity of conventional voltage criteria for left ventricular hypertrophy is decreased in obese persons and smokers. ECG evidence for left ventricular hypertrophy is a major noninvasive marker of increased risk of cardiovascular morbidity and mortality rates, including sudden cardiac death. However, because of false-positive and false-negative diagnoses, the ECG is of limited utility in diagnosing atrial or ventricular enlargement. More definitive information is provided by echocardiography (**Chap. 12**).

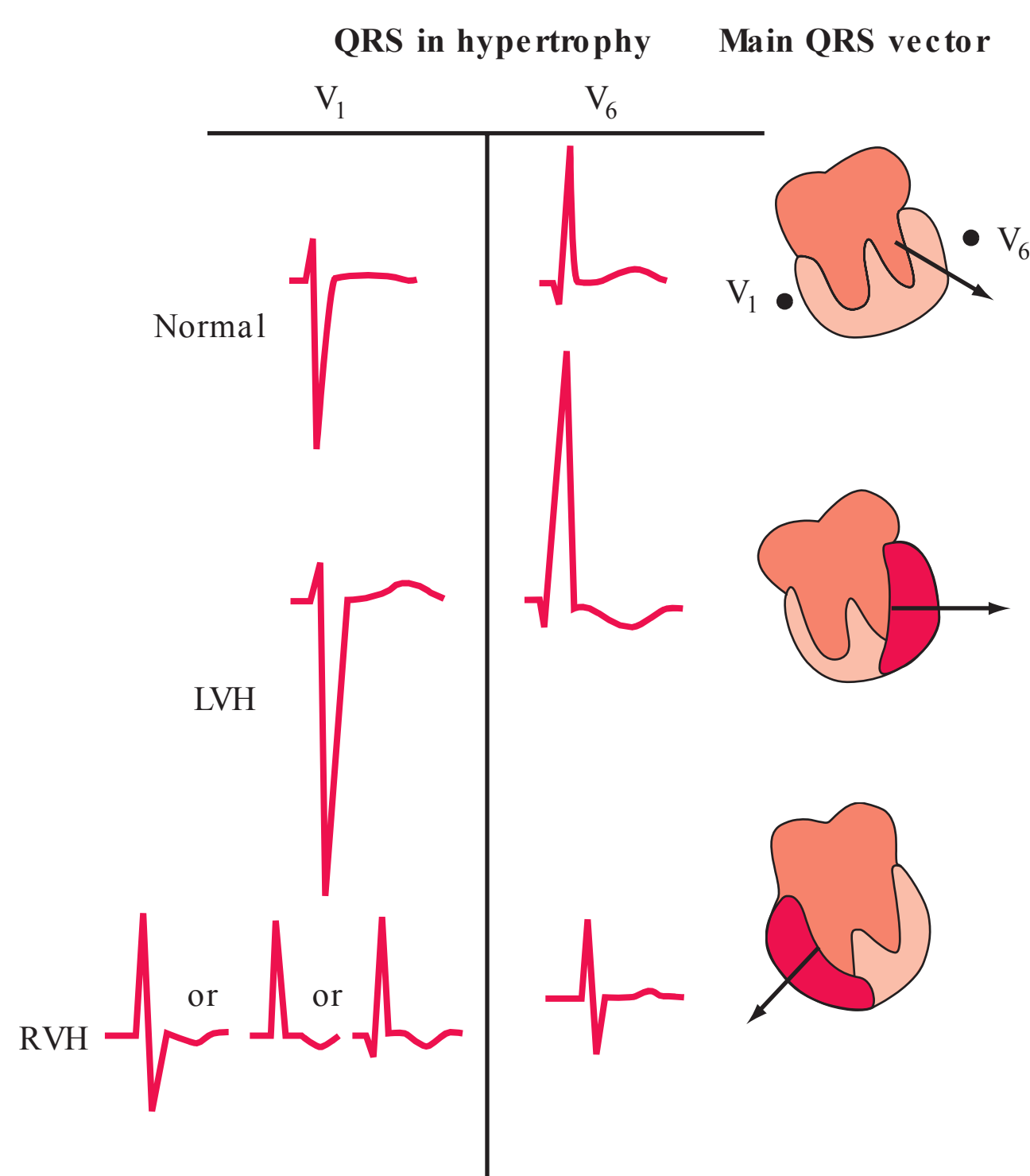


FIGURE 11-9

Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qR complex in lead V_1 . T-wave inversions may be present in right precordial leads.

BUNDLE BRANCH BLOCKS AND RELATED PATTERNS

Intrinsic impairment of conduction in either the right or the left bundle system (intraventricular conduction disturbances) leads to prolongation of the QRS interval. With complete bundle branch blocks, the QRS interval is $\geq 120 \text{ ms}$ in duration; with incomplete blocks, the QRS interval is between 100 and 120 ms. The QRS vector usually is oriented in the direction of the myocardial region where depolarization is delayed (**Fig. 11-10**). Thus, with right bundle branch block, the terminal QRS vector is oriented to the right and anteriorly (rSR' in V_1 and qRS in V_6 , typically). Left bundle branch block alters both early and later phases of ventricular depolarization. The major QRS vector is directed to the left and posteriorly. In addition, the normal early left-to-right pattern of septal activation is disrupted such that septal depolarization proceeds from right to left as well. As a result, left bundle branch block generates wide, predominantly negative (QS) complexes in lead V_1 and entirely positive (R) complexes in lead V_6 . A pattern identical to that of left bundle branch block, preceded by a sharp spike, is seen in most cases of electronic right ventricular pacing because of the relative delay in left ventricular activation.

Bundle branch block may occur in a variety of conditions. In subjects without structural heart disease, right bundle branch block is seen more commonly than left bundle branch block. Right bundle branch block also occurs with heart disease, both congenital (e.g., atrial septal defect) and acquired (e.g., valvular, ischemic). Left bundle branch block is often a marker of one of

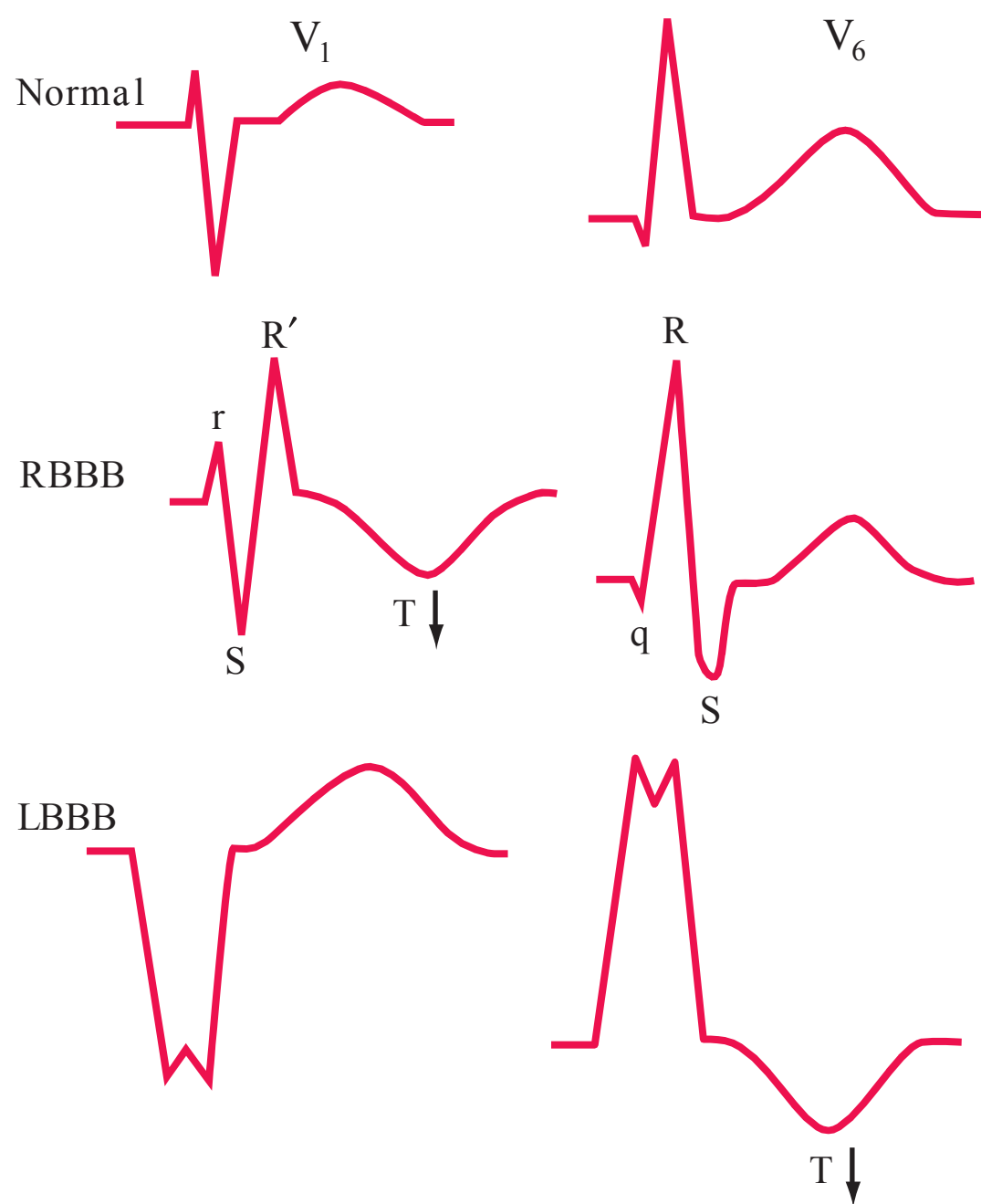


FIGURE 11-10

Comparison of typical QRS-T patterns in right bundle branch block (RBBB) and left bundle branch block (LBBB) with the normal pattern in leads V_1 and V_6 . Note the secondary T-wave inversions (arrows) in leads with an rSR' complex with RBBB and in leads with a wide R wave with LBBB.

four underlying conditions associated with increased risk of cardiovascular morbidity and mortality rates: coronary heart disease (frequently with impaired left ventricular function), hypertensive heart disease, aortic valve disease, and cardiomyopathy. Bundle branch blocks may be chronic or intermittent. A bundle branch block may be rate-related; for example, it often occurs when the heart rate exceeds some critical value.

Bundle branch blocks and depolarization abnormalities secondary to artificial pacemakers not only affect ventricular depolarization (QRS) but also are characteristically associated with secondary repolarization (ST-T) abnormalities. With bundle branch blocks, the T wave is typically opposite in polarity to the last deflection of the QRS (Fig. 11-10). T discordance of the QRS–T-wave vectors is caused by the altered sequence of repolarization that occurs secondary to altered depolarization. In contrast, primary repolarization abnormalities are independent of QRS changes and are related instead to actual alterations in the electrical properties of the myocardial fibers themselves (e.g., in the resting membrane potential or action potential duration), not just to changes in the sequence of repolarization. Ischemia, electrolyte imbalance, and drugs such as digoxin all cause such primary ST–T-wave changes. Primary and secondary T-wave changes may coexist. For example, T-wave inversions in the right precordial leads with left bundle branch block or in the left precordial

leads with right bundle branch block may be important markers of underlying ischemia or other abnormalities. A distinctive abnormality simulating right bundle branch block with ST-segment elevations in the right chest leads is seen with the Brugada pattern (**Chap. 17**).

Partial blocks (fascicular or “hemiblocks”) in the left bundle system (left anterior or posterior fascicular blocks) generally do not prolong the QRS duration substantially but instead are associated with shifts in the frontal plane QRS axis (leftward or rightward, respectively). Left anterior fascicular block (QRS axis more negative than -45°) is probably the most common cause of marked left axis deviation in adults. In contrast, left posterior fascicular block (QRS axis more rightward than $+110$ – 120°) is extremely rare as an isolated finding and requires exclusion of other factors causing right axis deviation mentioned earlier.

More complex combinations of fascicular and bundle branch blocks may occur that involve the left and right bundle system. Examples of bifascicular block include right bundle branch block and left posterior fascicular block, right bundle branch block with left anterior fascicular block, and complete left bundle branch block. Chronic bifascicular block in an asymptomatic individual is associated with a relatively low risk of progression to high-degree AV heart block. In contrast, new bifascicular block with acute anterior myocardial infarction carries a much greater risk of complete heart block. Alternation of right and left bundle branch block is a sign of trifascicular disease. However, the presence of a prolonged PR interval and bifascicular block does not necessarily indicate trifascicular involvement, since this combination may arise with AV node disease and bifascicular block. Intraventricular conduction delays also can be caused by extrinsic (toxic) factors that slow ventricular conduction, particularly hyperkalemia or drugs (e.g., class 1 antiarrhythmic agents, tricyclic antidepressants, phenothiazines).

Prolongation of QRS duration does not necessarily indicate a conduction delay but may be due to pre-excitation of the ventricles via a bypass tract, as in Wolff-Parkinson-White (WPW) patterns (**Chap. 17**) and related variants. The diagnostic triad of WPW consists of a wide QRS complex associated with a relatively short PR interval and slurring of the initial part of the QRS (delta wave), with the latter effect being due to aberrant activation of ventricular myocardium. The presence of a bypass tract predisposes to reentrant supraventricular tachyarrhythmias.

MYOCARDIAL ISCHEMIA AND INFARCTION

(See also **Chap. 41**) The ECG is a cornerstone in the diagnosis of acute and chronic ischemic heart disease. The findings depend on several key factors: the nature of the process (reversible [i.e., ischemia] versus irreversible

[i.e., infarction]), the duration (acute versus chronic), the extent (transmural versus subendocardial), and localization (anterior versus inferoposterior), as well as the presence of other underlying abnormalities (ventricular hypertrophy, conduction defects).

Ischemia exerts complex time-dependent effects on the electrical properties of myocardial cells. Severe, acute ischemia lowers the resting membrane potential and shortens the duration of the action potential. Such changes cause a voltage gradient between normal and ischemic zones. As a consequence, current flows between those regions. These currents of injury are represented on the surface ECG by deviation of the ST segment (**Fig. 11-11**). When the acute ischemia is transmural, the ST vector usually is shifted in the direction of the outer (epicardial) layers, producing ST elevations and sometimes, in the earliest stages of ischemia, tall, positive so-called hyperacute T waves over the ischemic zone. With ischemia confined primarily to the subendocardium, the ST vector typically shifts toward the subendocardium and ventricular cavity, so that overlying (e.g., anterior precordial) leads show ST-segment depression (with ST elevation in lead aVR). Multiple factors affect the amplitude of acute ischemic ST deviations. Profound ST elevation or depression in multiple leads usually indicates very severe ischemia. From a clinical viewpoint, the division of acute myocardial infarction into ST-segment elevation and non-ST elevation types is useful since the efficacy of acute reperfusion therapy is limited to the former group.

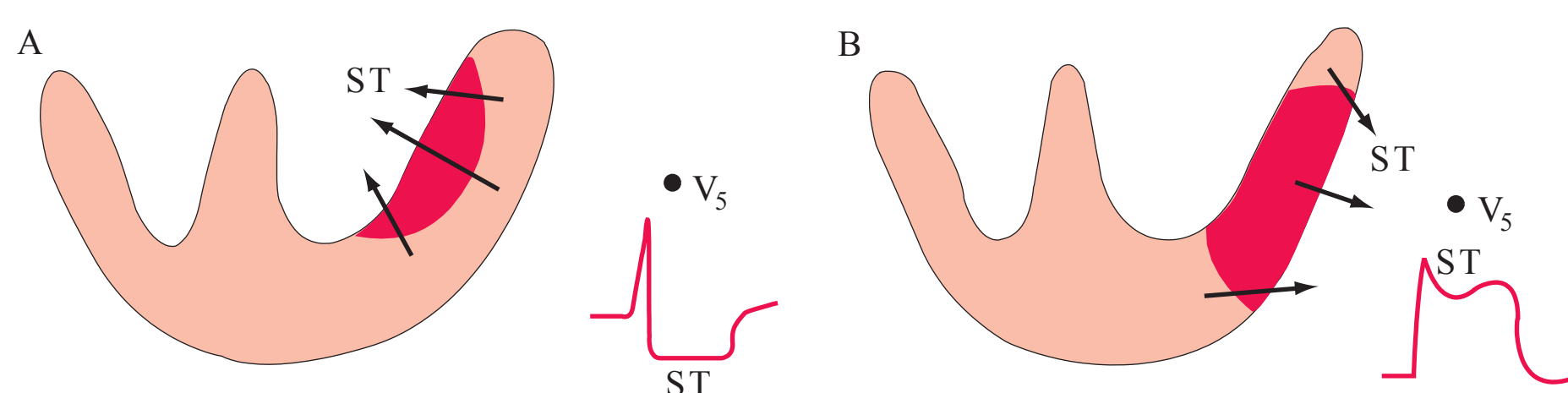


FIGURE 11-11

Acute ischemia causes a current of injury. With predominant subendocardial ischemia (A), the resultant ST vector will be directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore will record ST

depression. With ischemia involving the outer ventricular layer (B) (transmural or epicardial injury), the ST vector will be directed outward. Overlying leads will record ST elevation. The ECG leads are usually more helpful in localizing regions of ST elevation than non-ST elevation ischemia. For example, acute transmural anterior (including apical and lateral) wall ischemia is reflected by ST elevations or increased T-wave positivity in one or more of the precordial leads (V_1 – V_6) and leads I and aVL. Inferior wall ischemia produces changes in leads II, III, and aVF. “Posterior” wall ischemia (usually associated with lateral or inferior involvement) may be indirectly recognized by reciprocal ST depressions in leads V_1 to V_3 (thus constituting an ST elevation “equivalent” acute coronary syndrome). Right ventricular ischemia usually produces ST elevations in right-sided chest leads (**Fig. 11-5**). When ischemic ST elevations occur as the earliest sign of acute infarction, they typically are followed within a period ranging from hours to days by evolving T-wave inversions and often by Q waves occurring in the same lead distribution. Reversible transmural ischemia, for example, due to coronary vasospasm (Prinzmetal’s variant angina and possibly the Tako-tsubo “stress” cardiomyopathy syndrome), may cause transient ST-segment elevations without development of Q waves, as may very early reperfusion in acute coronary syndromes. Depending on the severity and duration of ischemia, the ST elevations may resolve completely in minutes or be followed by T-wave inversions that persist for hours or even days. Patients with ischemic chest pain who present with deep T-wave inversions in multiple precordial leads (e.g., V_1 – V_4 , I, and aVL) with or without cardiac enzyme elevations

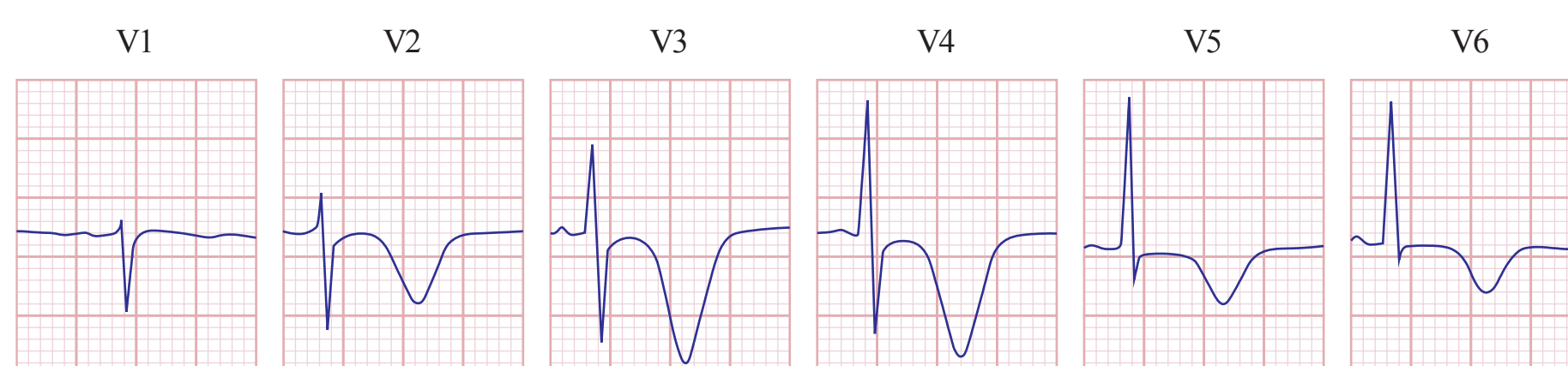


FIGURE 11-12

Severe anterior wall ischemia (with or without infarction) may cause prominent T-wave inversions in the precordial leads. This pattern (sometimes referred to as Wellens T waves) is

usually associated with a high-grade stenosis of the left anterior descending coronary artery.

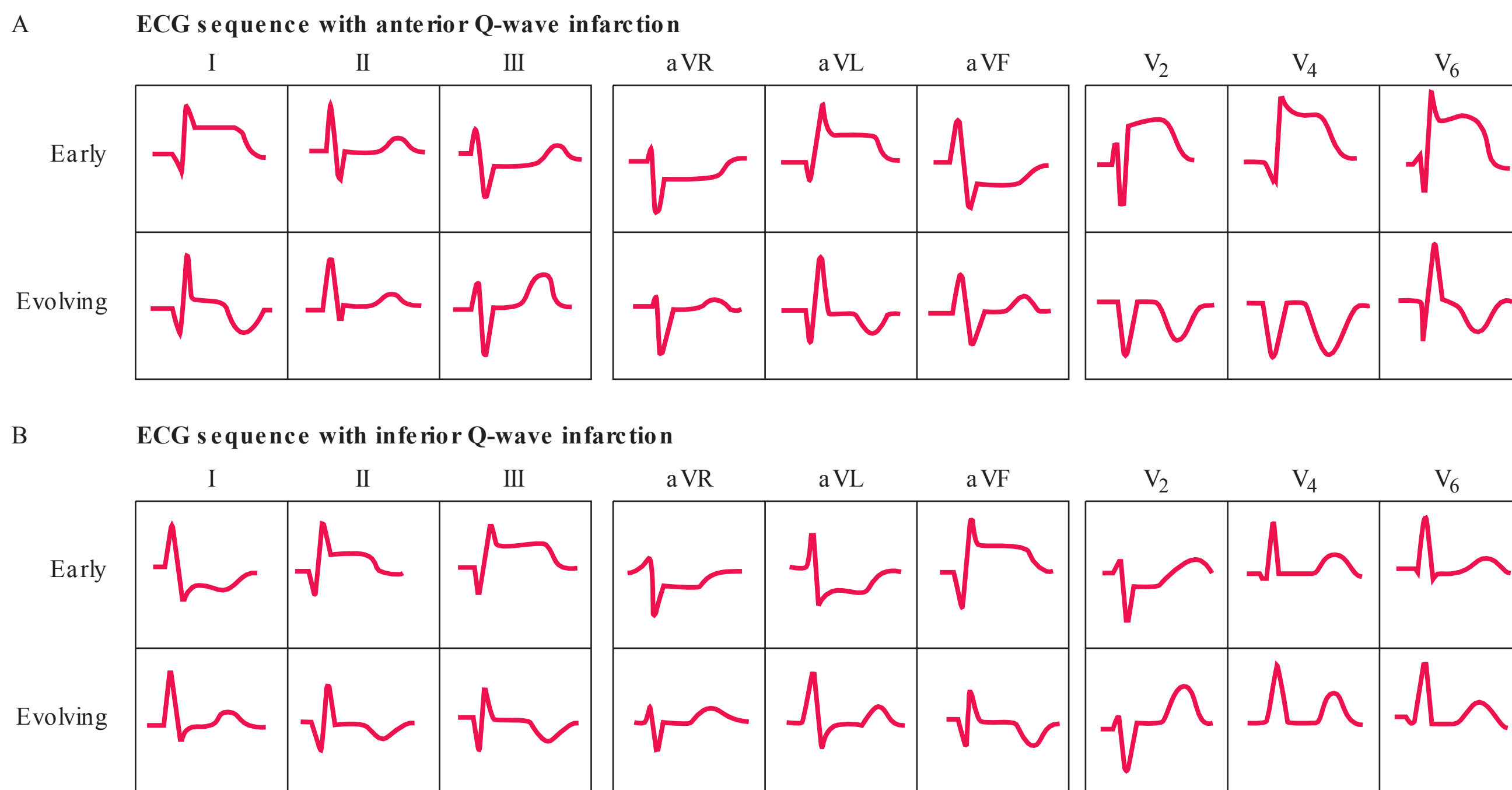


FIGURE 11-13

Sequence of depolarization and repolarization changes with (A) acute anterior and (B) acute inferior wall Q-wave infarctions. With anterior infarcts, ST elevation in leads I and aVL and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or

posterolateral) infarcts may be associated with reciprocal ST depressions in leads V₁ to V₃. (After AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.)

typically have severe obstruction in the left anterior descending coronary artery system (Fig. 11-12). In contrast, patients whose baseline ECG already shows abnormal T-wave inversions may develop T-wave normalization (pseudonormalization) during episodes of acute transmural ischemia.

With infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities. Necrosis of sufficient myocardial tissue may lead to decreased R-wave amplitude or abnormal Q waves (even in the absence of transmural) in the anterior or inferior leads (Fig. 11-13). Previously, abnormal Q waves were considered markers of transmural myocardial infarction, whereas subendocardial infarcts were thought not to produce Q waves. However, careful ECG-pathology correlative studies have indicated that transmural infarcts may occur without Q waves and that subendocardial (nontransmural) infarcts sometimes may be associated with Q waves. Therefore, infarcts are more appropriately classified as “Q-wave” or “non-Q-wave.” The major acute ECG changes in syndromes of ischemic heart disease are summarized schematically in Fig. 11-14. Loss of depolarization forces due to posterior or lateral infarction may cause reciprocal increases in R-wave amplitude in leads V₁ and V₂ without diagnostic Q waves in any of the conventional leads. Atrial infarction may be associated with PR-segment deviations due

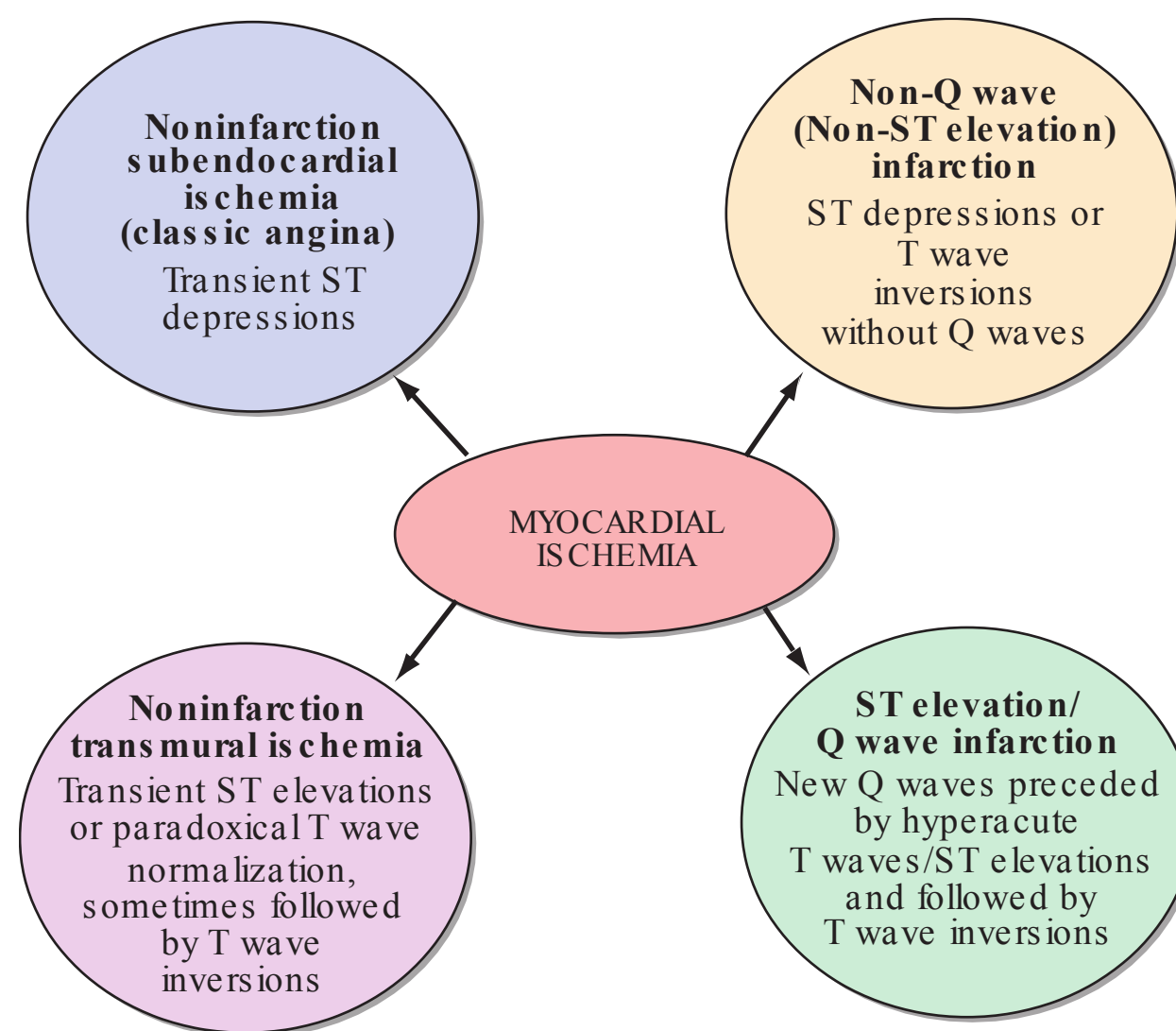


FIGURE 11-14

Variability of ECG patterns with acute myocardial ischemia. The ECG also may be normal or nonspecifically abnormal. Furthermore, these categorizations are not mutually exclusive. (After AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.)

to an atrial current of injury, changes in P-wave morphology, or atrial arrhythmias. In the weeks and months after infarction, these ECG changes may persist or begin to resolve. Complete normalization of the ECG after

Q-wave infarction is uncommon but may occur, particularly with smaller infarcts. In contrast, ST-segment elevations that persist for several weeks or more after a Q-wave infarct usually correlate with a severe underlying wall motion disorder (akinetic or dyskinetic zone), although not necessarily a frank ventricular aneurysm. ECG changes due to ischemia may occur spontaneously or may be provoked by various exercise protocols (stress electrocardiography; **Chap. 39**).

The ECG has important limitations in both sensitivity and specificity in the diagnosis of ischemic heart disease. Although a single normal ECG does not exclude ischemia or even acute infarction, a normal ECG throughout the course of an acute infarct is distinctly uncommon. Prolonged chest pain without diagnostic ECG changes therefore should always prompt a careful search for other noncoronary causes of chest pain (**Chap. 4**). Furthermore, the diagnostic changes of acute or evolving ischemia are often masked by the presence of left bundle branch block, electronic ventricular pacemaker patterns, and Wolff-Parkinson-White preexcitation. However, clinicians continue to overdiagnose ischemia or infarction based on the presence of ST-segment elevations or depressions; T-wave inversions; tall, positive T waves; or Q waves not related to ischemic heart disease (pseudoinfarct patterns). For example, ST-segment elevations simulating ischemia may occur with acute pericarditis or myocarditis, as a normal variant (including the typical “early repolarization” pattern), or in a variety of other conditions (**Table 11-1**). Similarly, tall, positive T waves do not invariably represent hyperacute ischemic changes but may also be caused by normal variants, hyperkalemia, cerebrovascular injury, and left ventricular volume overload due to mitral or aortic regurgitation, among other causes.

ST-segment elevations and tall, positive T waves are common findings in leads V_1 and V_2 in left bundle branch block or left ventricular hypertrophy in the absence of ischemia. The differential diagnosis of Q waves includes physiologic or positional variants, ventricular hypertrophy, acute or chronic noncoronary myocardial injury, hypertrophic cardiomyopathy, and ventricular conduction disorders. Digoxin, ventricular hypertrophy, hypokalemia, and a variety of other factors may cause ST-segment depression mimicking subendocardial ischemia. Prominent T-wave inversion may occur with ventricular hypertrophy, cardiomyopathies, myocarditis, and cerebrovascular injury (particularly intracranial bleeds), among many other conditions.

METABOLIC FACTORS AND DRUG EFFECTS

A variety of metabolic and pharmacologic agents alter the ECG and, in particular, cause changes in repolarization (ST-T-U) and sometimes QRS prolongation.

TABLE 11-1

DIFFERENTIAL DIAGNOSIS OF ST-SEGMENT ELEVATIONS

Ischemia/myocardial infarction
Noninfarction, transmural ischemia (Prinzmetal’s angina, and probably Tako-tsubo syndrome, which may also exactly simulate classical acute infarction)
Acute myocardial infarction
Postmyocardial infarction (ventricular aneurysm pattern)
Acute pericarditis
Normal variants (including benign “early repolarization” patterns)
Left ventricular hypertrophy/left bundle branch block ^a
Other (rarer)
Acute pulmonary embolism ^a
Brugada patterns (right bundle branch block–like pattern with ST elevations in right precordial leads) ^a
Class 1C antiarrhythmic drugs ^a
DC cardioversion
Hypercalcemia ^a
Hyperkalemia ^a
Hypothermia (J [Osborn] waves)
Nonischemic myocardial injury
Myocarditis
Tumor invading left ventricle
Trauma to ventricles

^aUsually localized to V_1 – V_2 or V_3 .

Source: Modified from AL Goldberger et al: Goldberger’s Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.

Certain life-threatening electrolyte disturbances may be diagnosed initially and monitored from the ECG. Hyperkalemia produces a sequence of changes (**Fig. 11-15**), usually beginning with narrowing and peaking (tenting) of the T waves. Further elevation of extracellular K^+ leads to AV conduction disturbances, diminution in P-wave amplitude, and widening of the QRS interval. Severe hyperkalemia eventually causes cardiac arrest with a slow sinusoidal type of mechanism (“sine-wave” pattern) followed by asystole. Hypokalemia (**Fig. 11-16**) prolongs ventricular repolarization, often with prominent U waves. Prolongation of the QT interval is also seen with drugs that increase the duration of the ventricular action potential: class 1A antiarrhythmic agents and related drugs (e.g., quinidine, disopyramide, procainamide, tricyclic antidepressants, phenothiazines) and class III agents (e.g., amiodarone [Fig. 11-16], dofetilide, dronedarone, sotalol, ibutilide). Marked QT prolongation, sometimes with deep, wide T-wave inversions, may occur with intracranial bleeds, particularly subarachnoid hemorrhage (“CVA

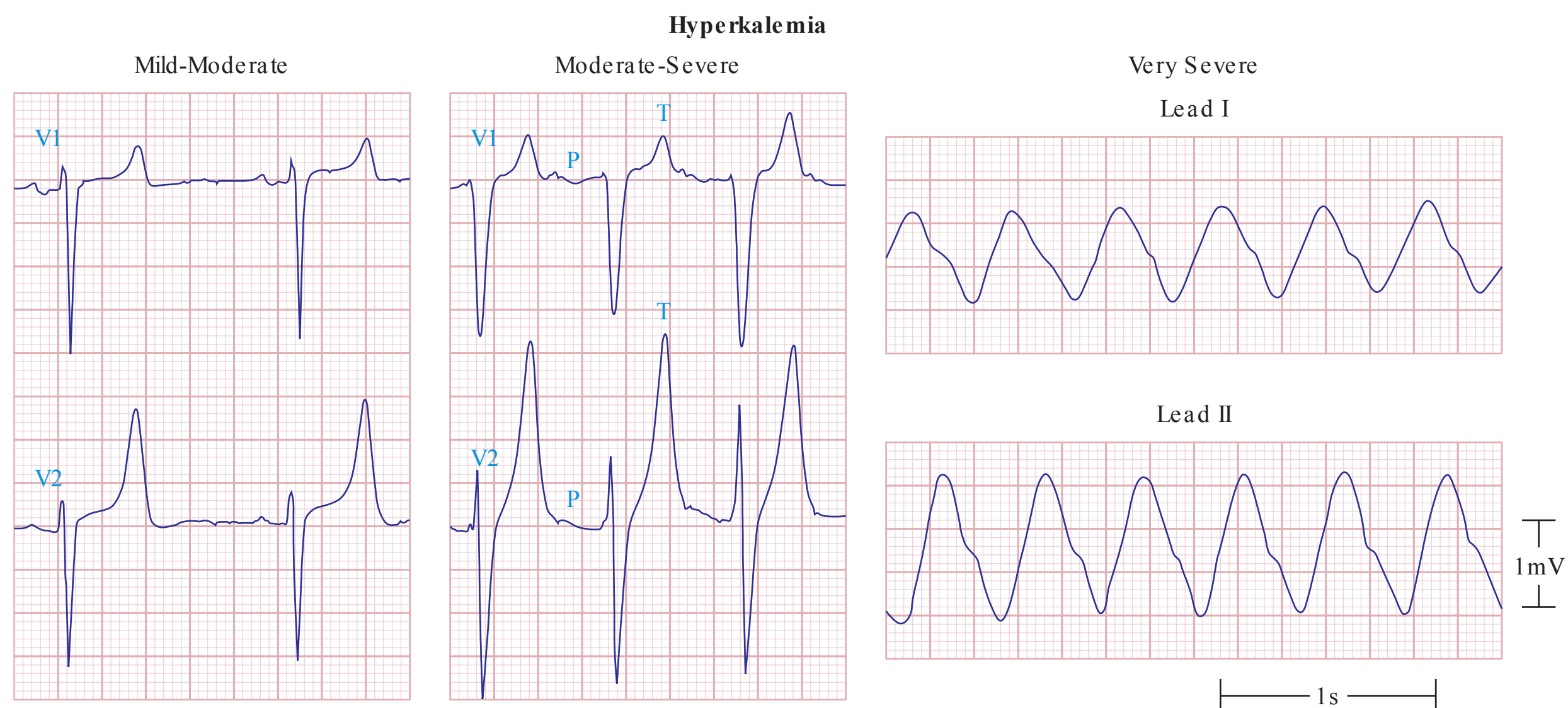


FIGURE 11-15

The earliest ECG change with hyperkalemia is usually peaking (“tenting”) of the T waves. With further increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine-wave

pattern leads to asystole unless emergency therapy is given. (After ALGoldberger et al: Goldberger’s Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.)

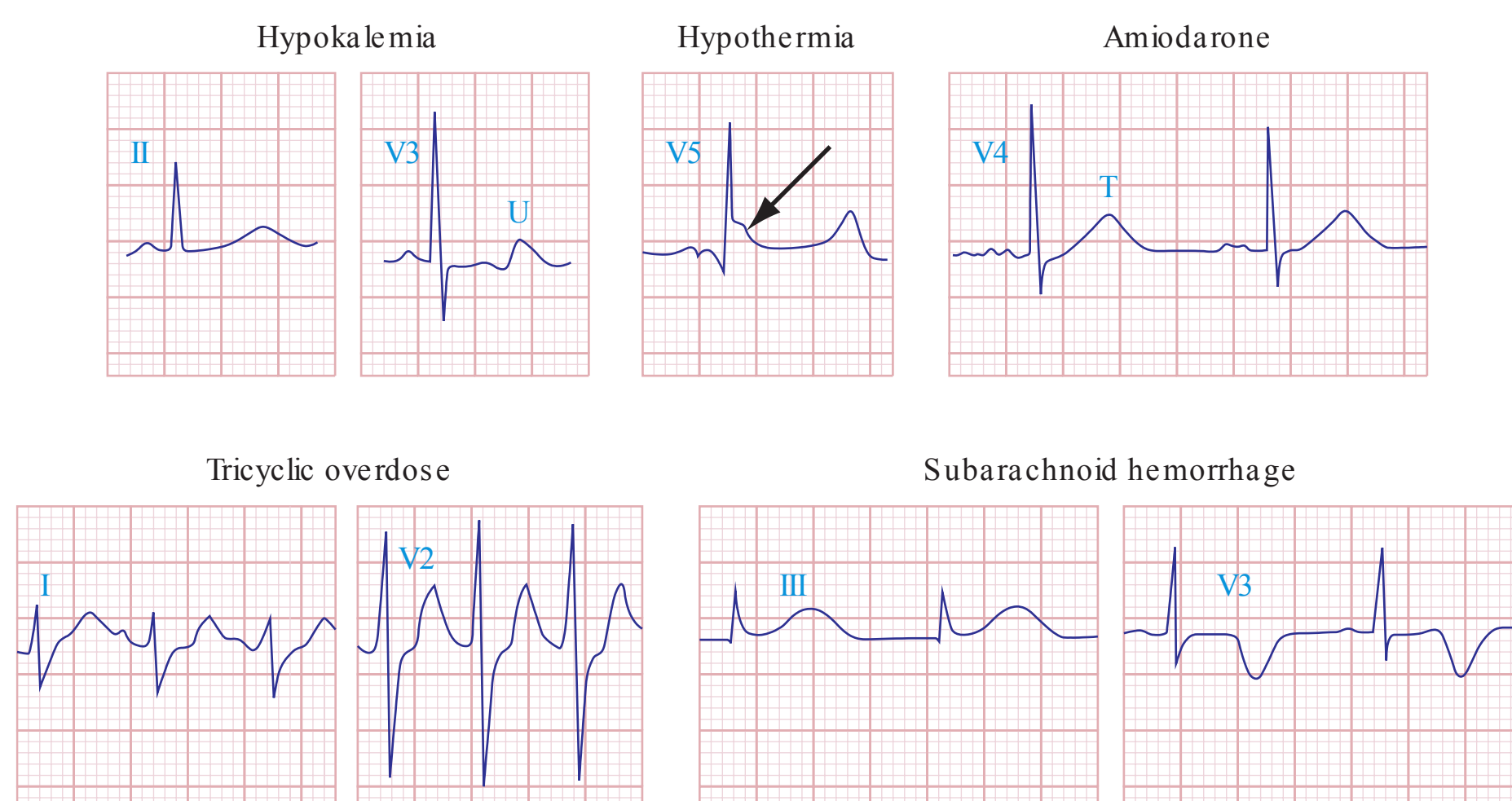


FIGURE 11-16

A variety of metabolic derangements, drug effects, and other factors may prolong ventricular repolarization with QT prolongation or prominent U waves. Prominent repolarization prolongation, particularly if due to hypokalemia, inherited “channelopathies,” or certain pharmacologic agents, indicates increased susceptibility to torsades des pointes–type ventricular tachycardia

(Chap. 18). Marked systemic hypothermia is associated with a distinctive convex “hump” at the J point (Osborn wave, arrow) due to altered ventricular action potential characteristics. Note QRS and QT prolongation along with sinus tachycardia in the case of tricyclic antidepressant overdose.

T-wave” pattern) (Fig. 11-16). Systemic hypothermia also prolongs repolarization, usually with a distinctive convex elevation of the J point (Osborn wave). Hypocalcemia typically prolongs the QT interval (ST portion), whereas hypercalcemia shortens it (Fig. 11-17). Digitalis glycosides also shorten the QT interval, often with a characteristic “scooping” of the ST–T-wave complex (digitalis effect).

Many other factors are associated with ECG changes, particularly alterations in ventricular repolarization. T-wave flattening, minimal T-wave inversions, or slight ST-segment depression (“nonspecific ST–T-wave changes”) may occur with a variety of electrolyte and acid-base disturbances, a number of infectious processes, central nervous system disorders, endocrine abnormalities, many drugs, ischemia, hypoxia, and

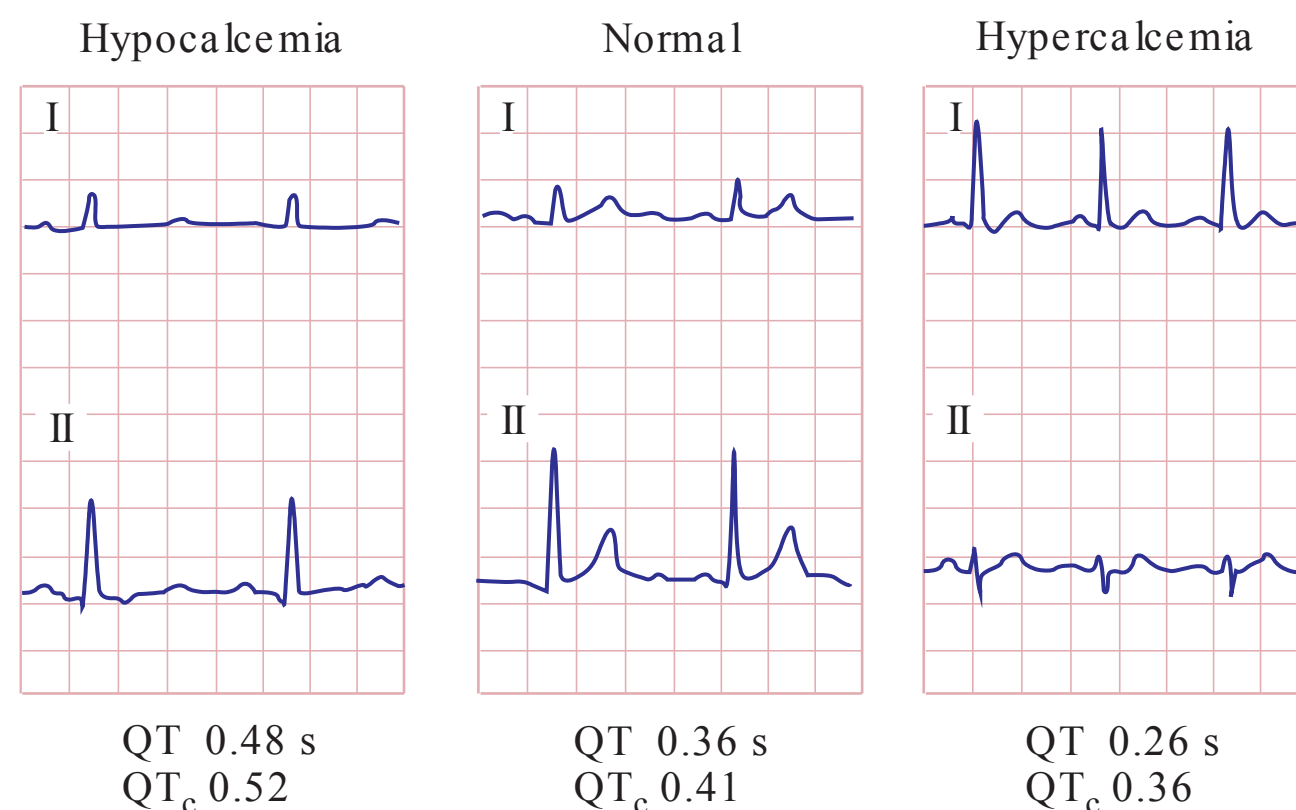


FIGURE 11-17

Prolongation of the Q-T interval (ST-segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment and shortening of the QT interval.

virtually any type of cardiopulmonary abnormality. Although subtle ST-T-wave changes may be markers of ischemia, transient nonspecific repolarization changes may also occur after a meal or with postural (orthostatic) change, hyperventilation, or exercise in healthy individuals.

LOW QRS VOLTAGE

Low QRS voltage is arbitrarily defined as peak-to-trough QRS amplitudes of ≤ 5 mm in the six limb leads and/or ≤ 10 mm in the chest leads. Multiple factors may be responsible. Among the most serious include pericardial (Fig. 11-18) or pleural effusions, chronic

obstructive pulmonary disease, infiltrative cardiomyopathies, and anasarca.

ELECTRICAL ALTERNANS

Electrical alternans—a beat-to-beat alternation in one or more components of the ECG signal—is a common type of nonlinear cardiovascular response to a variety of hemodynamic and electrophysiologic perturbations. Total electrical alternans (P-QRS-T) with sinus tachycardia is a relatively specific sign of pericardial effusion, usually with cardiac tamponade (Fig. 11-18). The mechanism relates to a periodic swinging motion of the heart in the effusion at a frequency exactly one-half the heart rate. In contrast, pure repolarization (ST-T or U wave) alternans is a sign of electrical instability and may precede ventricular tachyarrhythmias.

CLINICAL INTERPRETATION OF THE ECG

Accurate analysis of ECGs requires thoroughness and care. The patient's age, gender, and clinical status should always be taken into account. Many mistakes in ECG interpretation are errors of omission. Therefore, a systematic approach is essential. The following 14 points should be analyzed carefully in every ECG: (1) standardization (calibration) and technical features (including lead placement and artifacts), (2) rhythm, (3) heart rate, (4) PR interval/AV conduction, (5) QRS interval, (6) QT/QT_c intervals, (7) mean QRS electrical axis, (8) P waves, (9) QRS voltages, (10) precordial R-wave progression, (11) abnormal Q waves, (12) ST segments,

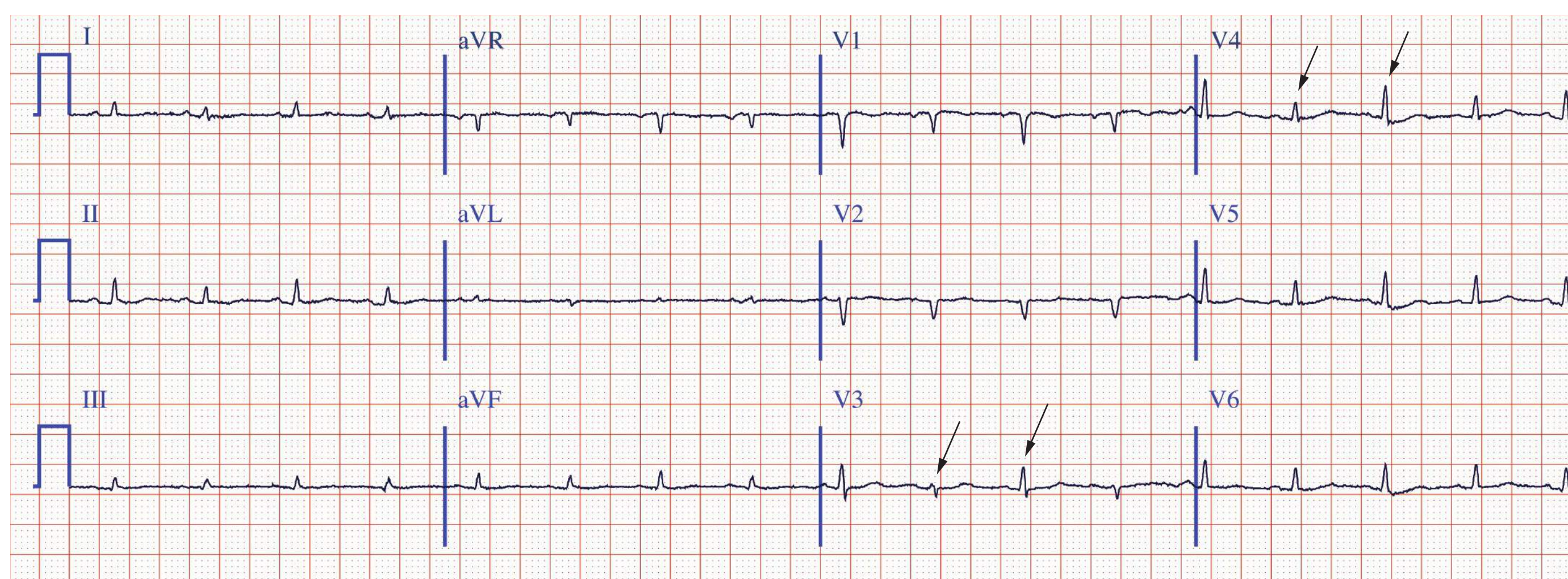


FIGURE 11-18

Classic triad of findings for pericardial effusion with cardiac tamponade: (1) sinus tachycardia; (2) low QRS voltages; and (3) electrical alternans (best seen in leads V₃ and V₄ in this case; arrows).

This triad is highly specific for pericardial effusion, usually with tamponade physiology, but of limited sensitivity. (Adapted from LA Nathanson et al: ECG Wave-Maven. <http://ecg.bidmc.harvard.edu>.)

(13) T waves, and (14) U waves. Comparison with any previous ECGs is invaluable. **The diagnosis and management of specific cardiac arrhythmias and conduction disturbances are discussed in Chaps. 15 and 17.**

COMPUTERIZED ELECTROCARDIOGRAPHY

Computerized ECG systems are widely used for immediate retrieval of thousands of ECG records. Computer

interpretation of ECGs still has major limitations. Incomplete or inaccurate readings are most likely with arrhythmias and complex abnormalities. Therefore, computerized interpretation (including measurements of basic ECG intervals) should not be accepted without careful clinician review.

CHAPTER 12

NONINVASIVE CARDIAC IMAGING: ECHOCARDIOGRAPHY, NUCLEAR CARDIOLOGY, AND MAGNETIC RESONANCE/COMPUTED TOMOGRAPHY IMAGING



Marcelo F. Di Carli ■ Raymond Y. Kwong ■ Scott D. Solomon

The ability to image the heart and blood vessels non-invasively has been one of the greatest advances in cardiovascular medicine since the development of the electrocardiogram. Cardiac imaging complements history taking and physical examination, blood and laboratory testing, and exercise testing in the diagnosis and management of most diseases of the cardiovascular system. Modern cardiovascular imaging consists of echocardiography (cardiac ultrasound), nuclear scintigraphy including positron emission tomography (PET) imaging, magnetic resonance imaging (MRI), and computed tomography (CT). These studies, often used in conjunction with exercise testing, can be used independently or in concert depending on the specific diagnostic needs. In this chapter, we review the principles of each of these modalities and the utility and relative benefits of each for the most common cardiovascular diseases.

PRINCIPLES OF MULTIMODALITY CARDIAC IMAGING

ECHOCARDIOGRAPHY

Echocardiography uses high-frequency sound waves (ultrasound) to penetrate the body, reflect from relevant structures, and generate an image. The basic physical principles of echocardiography are identical to other types of ultrasound imaging, although the hardware and software are optimized for evaluation of cardiac structure and function. Early echocardiography machines

displayed “M-mode” echocardiograms in which a single ultrasound beam was displayed over time on a moving sheet of paper (Fig. 12-1, left panel). Modern echocardiographic machinery uses phased array transducers that contain up to 512 elements and emit ultrasound in sequence. The reflected ultrasound is then sensed by the receiving elements. A “scan converter” uses information about the timing and magnitude of the reflected ultrasound to generate an image (Fig. 12-1, right panel). This sequence happens repeatedly in “real time” to generate moving images with frame rates that are typically greater than 30 frames per second, but can exceed 100 frames per second. The gray scale of the image features indicates the intensity of the reflected ultrasound; fluid or blood appears black, and highly reflective structures, such as calcifications on cardiac valves or the pericardium, appear white. Tissues such as myocardium appear more gray, and tissues such as muscle display a unique speckle pattern. Although M-mode echocardiography has largely been supplanted by two-dimensional echocardiography, it is still used because of its high temporal resolution and accuracy for making linear measurements.

The spatial resolution of ultrasound is dependent on the wavelength: the smaller the wavelength and the higher the frequency of the ultrasound beam, the greater are the spatial resolution and ability to discern small structures. Increasing the frequency of ultrasound will increase resolution but at the expense of reduced penetration. Higher frequencies can be used in pediatric imaging or transesophageal echocardiography where the transducer can be much closer to the structures being interrogated, and this is a rationale for using

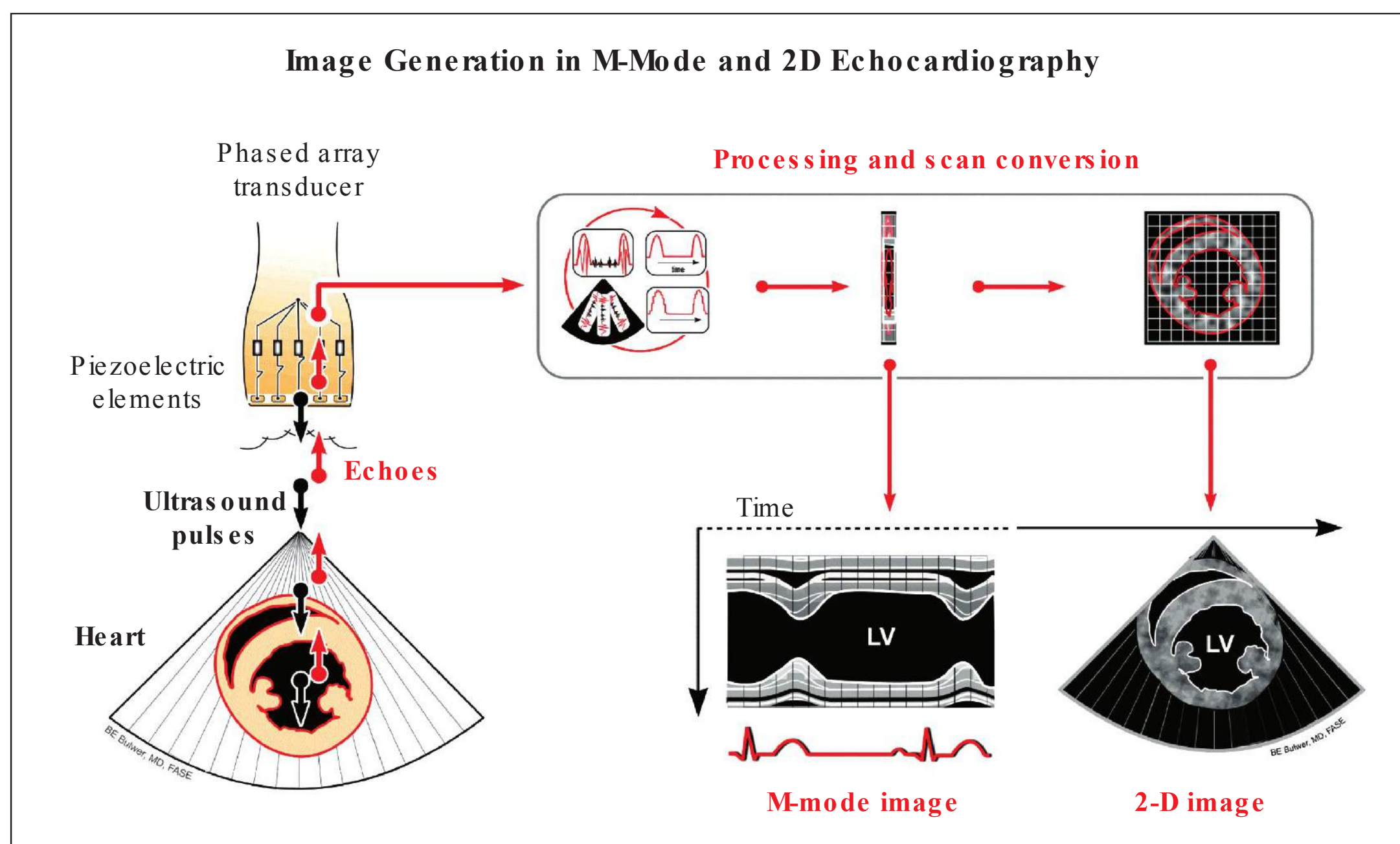


FIGURE 12-1

Principle of image generation in two-dimensional (2D) echocardiography. An electronically steerable phased-array transducer emits ultrasound from piezoelectric elements, and returning echoes are used to generate a 2D image (right) using

a scan converter. Early echocardiography machines used a single ultrasound beam to generate an “M-mode” echocardiogram (see text), although modern equipment generates M-mode echocardiograms digitally from the 2D data. LV, left ventricle.

transesophageal echocardiography to obtain higher quality images.

Three-dimensional ultrasound transducers use a waffle-like matrix array transducer and receive a pyramidal data sector. Three-dimensional echocardiography is being increasingly used for assessment of congenital heart disease and valves, although current image quality lags behind two-dimensional ultrasound (**Fig. 12-2**).

In addition to the generation of two-dimensional images that provide information about cardiac structure

and function, echocardiography can be used to interrogate blood flow within the heart and blood vessels by using the Doppler principle to ascertain the velocity of blood flow. When ultrasound emitted from a transducer reflects off red blood cells that are moving toward the transducer, the reflected ultrasound will return at a slightly higher frequency than emitted; the opposite is true when flow is away from the transducer. The frequency difference, termed the Doppler shift, is directly related to the velocity of the flow of the red blood cells. The velocity of blood flow between two chambers will be directly related to the pressure gradient between those chambers. A modified form of the Bernoulli equation, $p = 4v^2$

where p = the pressure gradient and v = the velocity of blood flow in meters per second, can be used to calculate this pressure gradient in the majority of clinical circumstances. This principle can be used to determine the pressure gradient between chambers and across valves and has become central to the quantitative assessment of valvular heart disease.

There are three types of Doppler ultrasound that are typically used in standard echocardiographic examinations: spectral Doppler, which consists of both pulsed wave Doppler and continuous wave Doppler, and color flow Doppler. Both types of spectral Doppler will display a waveform representing the velocity of blood flow, with time on the horizontal axis and velocity on

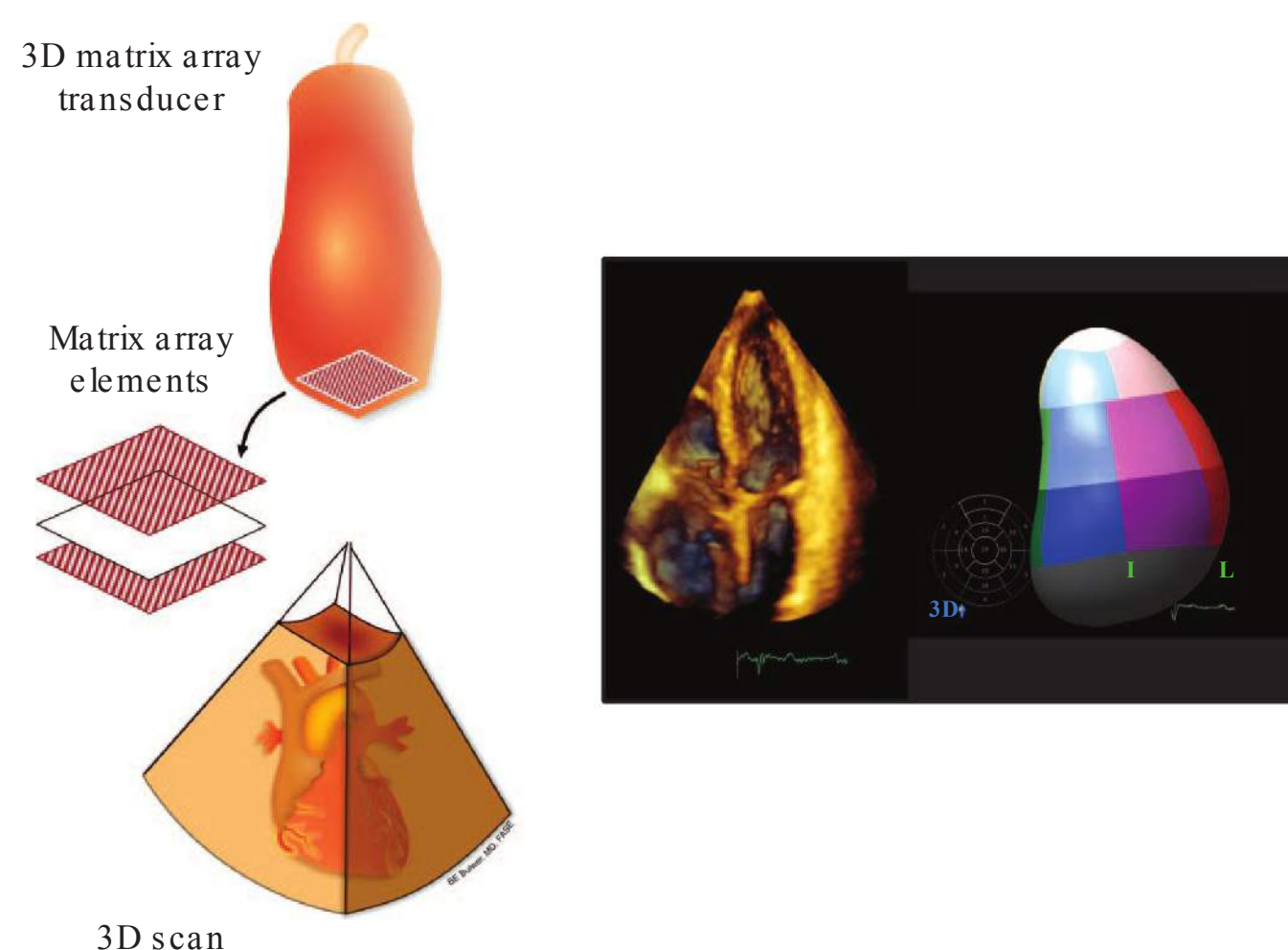


FIGURE 12-2

Three-dimensional (3D) probe and 3D image.

the vertical axis. Pulsed wave Doppler is used to interrogate relatively low velocity flow and has the ability to determine blood flow velocity at a particular location within the heart. Continuous wave Doppler is used to assess high-velocity flow but can only identify the highest velocity in a particular direction and cannot interrogate the velocity at a specific depth location. Both of these techniques can only accurately assess velocities that are in the direction of the ultrasound scan lines, and velocities that are at an angle to the direction of the ultrasound beam will be underestimated. Color flow Doppler is a form of pulsed wave Doppler in which the velocity of blood flow is color encoded according to a scale and superimposed on a two-dimensional grayscale image in real time, giving the appearance of real-time flow within the heart. The Doppler principle can also be used to assess the velocity of myocardial motion, which is a sensitive way to assess myocardial function (**Fig. 12-3**). A standard full transthoracic echocardiographic examination consists of a series of two-dimensional views made up of different imaging planes from various scanning locations and spectral and color flow Doppler assessment.

Transesophageal echocardiography is a form of echocardiography in which the transducer is located on the tip of an endoscope that can be inserted into the esophagus. This procedure allows closer, less obstructed views of cardiac structures, without having to penetrate through chest wall, muscle, and ribs. Because less penetration is needed, a higher frequency probe can be used, and image quality and spatial resolution are generally higher than with standard transthoracic imaging, particularly for structures that are more posterior. Transesophageal echocardiography has become the test of choice for assessment of small lesions in the heart such as valvular vegetations, especially in the setting

of a prosthetic valve disease, and intracardiac thrombi, including assessment of the left atrial appendage, which is difficult to visualize with standard transthoracic imaging, and for assessment of congenital abnormalities. Transesophageal echocardiography requires both topical and systemic anesthesia, generally conscious sedation, and carries additional risks such as potential damage to the esophagus, including the rare possibility of perforation, aspiration, and anesthesia-related complications. Patients generally need to give consent for transesophageal echocardiography and be monitored during and subsequent to the procedure. Transesophageal echocardiography can be carried out in intubated patients and is routinely used for intraoperative monitoring during cardiac surgery.

Stress echocardiography is routinely used to assess cardiac function during exercise and can be used to identify myocardial ischemia or to assess valvular function under exercise conditions. Stress echocardiography is typically performed in conjunction with treadmill or bicycle exercise testing, but can also be performed using pharmacologic stress most typically with an intravenous infusion of dobutamine (see section on stress imaging below).

Whereas typical echocardiographic equipment is large, bulky, and expensive, small hand-held ultrasound equipment developed over the last decade now offers diagnostic quality imaging in a package small enough to be carried on rounds (**Fig. 12-4**). These relatively inexpensive point-of-care devices currently lack full diagnostic capabilities but represent an excellent screening tool if used by an experienced operator. As these units become even smaller and less expensive, they are being increasingly used not just by cardiologists, but also by emergency medicine physicians, intensivists, anesthesiologists, and internists.

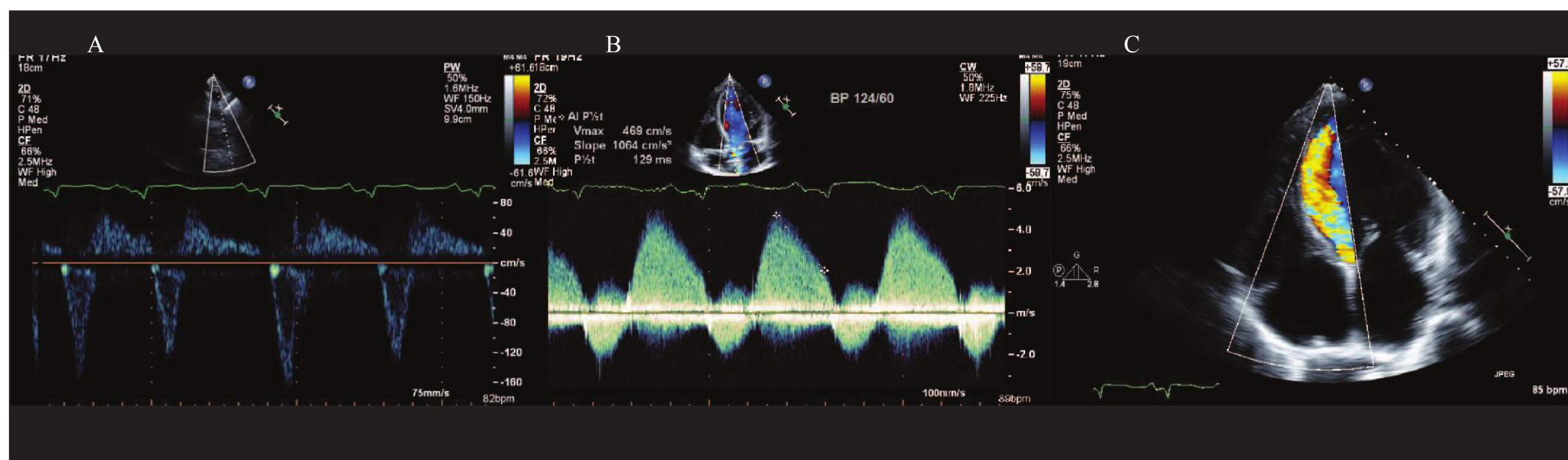


FIGURE 12-3

Three types of Doppler ultrasound. A and B. Pulsed and continuous wave Doppler waveforms with time on horizontal axis and velocity of blood flow on vertical axis. C. Color flow

Doppler, where velocities are encoded by colors according to scale on right side of screen and superimposed on a two-dimensional grayscale image.



FIGURE 12-4
Two examples of hand-held ultrasound equipment: V-Scan (General Electric, left) and Sonosite (right).

RADIONUCLIDE IMAGING

Radionuclide imaging techniques are commonly used for the evaluation of patients with known or suspected coronary artery disease (CAD), including for initial diagnosis and risk stratification as well as the assessment of myocardial viability. These techniques use small amounts of radiopharmaceuticals (Table 12-1), which are injected intravenously and trapped in the heart and/or vascular cells. Radioactivity within the heart and vasculature decays by emitting gamma rays. The interaction between these gamma rays and the detectors in specialized scanners (single-photon emission computed tomography [SPECT] and PET) creates a scintillation event or light output, which can be captured by digital recording equipment to form an image of the heart and vasculature. Like CT and MRI, radionuclide images also generate tomographic (three-dimensional) views of the heart and vasculature.

Radiopharmaceuticals used in clinical imaging

Table 12-1 summarizes the most commonly used radiopharmaceuticals in clinical SPECT and PET imaging.

Protocols for stress myocardial perfusion imaging

Both exercise and pharmacologic stress can be used for myocardial perfusion imaging. Exercise stress is generally preferred because it is physiologic and provides additional clinically important information (i.e., clinical and hemodynamic responses, ST-segment changes, exercise duration, and functional status). However, submaximal effort will lower the sensitivity of the test and should be avoided, especially if the test is requested for initial diagnosis of CAD. In patients who are unable to exercise or who exercise submaximally, pharmacologic stress offers an adequate alternative to exercise stress

TABLE 12-1

RADIOPHARMACEUTICALS FOR CLINICAL NUCLEAR CARDIOLOGY			
RADIOPHARMACEUTICAL	IMAGING TECHNIQUE	PHYSICAL HALF-LIFE	APPLICATION
Technetium-99m sestamibi	SPECT	6 h	Myocardial perfusion imaging
Technetium-99m tetrofosmin	SPECT	6 h	Myocardial perfusion imaging
Thallium-201	SPECT	72 h	Myocardial perfusion imaging
Iodine-123 metaiodobenzyl-guanidine (MIBG)	SPECT	13 h	Cardiac sympathetic innervation
Rubidium-82	PET	76 s	Myocardial perfusion imaging
¹³ N-ammonia	PET	10 min	Myocardial perfusion imaging
¹⁸ F-fluorodeoxyglucose	PET	110 min	Myocardial viability and inflammation imaging

Abbreviations: PET, positron emission tomography; SPECT, single-photon emission computed tomography.

testing. Pharmacologic stress can be accomplished either with coronary vasodilators, such as adenosine, dipyridamole, or regadenoson, or β_1 -receptor agonists, such as dobutamine. For patients unable to exercise, vasodilators are the most commonly used stressors in combination with myocardial perfusion imaging. Dobutamine is a potent β_1 -receptor agonist that increases myocardial oxygen demand by augmenting contractility, heart rate, and blood pressure similar to exercise. It is generally used as an alternative to vasodilator stress in patients with chronic pulmonary disease, in whom vasodilators may be contraindicated. Dobutamine is also commonly used as a pharmacologic alternative to stress testing in stress echocardiography.

Myocardial perfusion and viability imaging protocols

Imaging protocols are tailored to the individual patient based on the clinical question, patient's risk, ability to exercise, body mass index, and other factors.

For SPECT imaging, technetium-99m (^{99m}Tc)-labeled tracers are the most commonly used imaging

agents because they are associated with the best image quality and the lowest radiation dose to the patient (**Fig. 12-5**). Selection of the protocol (stress-only, single-day, or 2-day) depends on the patient and clinical question. After intravenous injection, myocardial uptake of ^{99m}Tc -labeled tracers is rapid (1–2 min). After uptake, these tracers become trapped intracellularly in mitochondria and show minimal change over time. This is why ^{99m}Tc tracers can be helpful in patients with chest pain of unclear etiology occurring at rest, because patients can be injected while having chest pain and imaged some time later after symptoms subside. Because the radiotracer is trapped at the time of injection, the images provide a snapshot of myocardial perfusion at the time of injection, even if the acquisition is delayed. Indeed, a normal myocardial perfusion study following a rest injection in a patient with active chest pain effectively excludes myocardial ischemia as the cause of chest pain (high negative predictive value). While used commonly in the past for perfusion imaging, thallium-201 protocols are now rarely used because they are typically associated with a higher radiation dose to the patient.

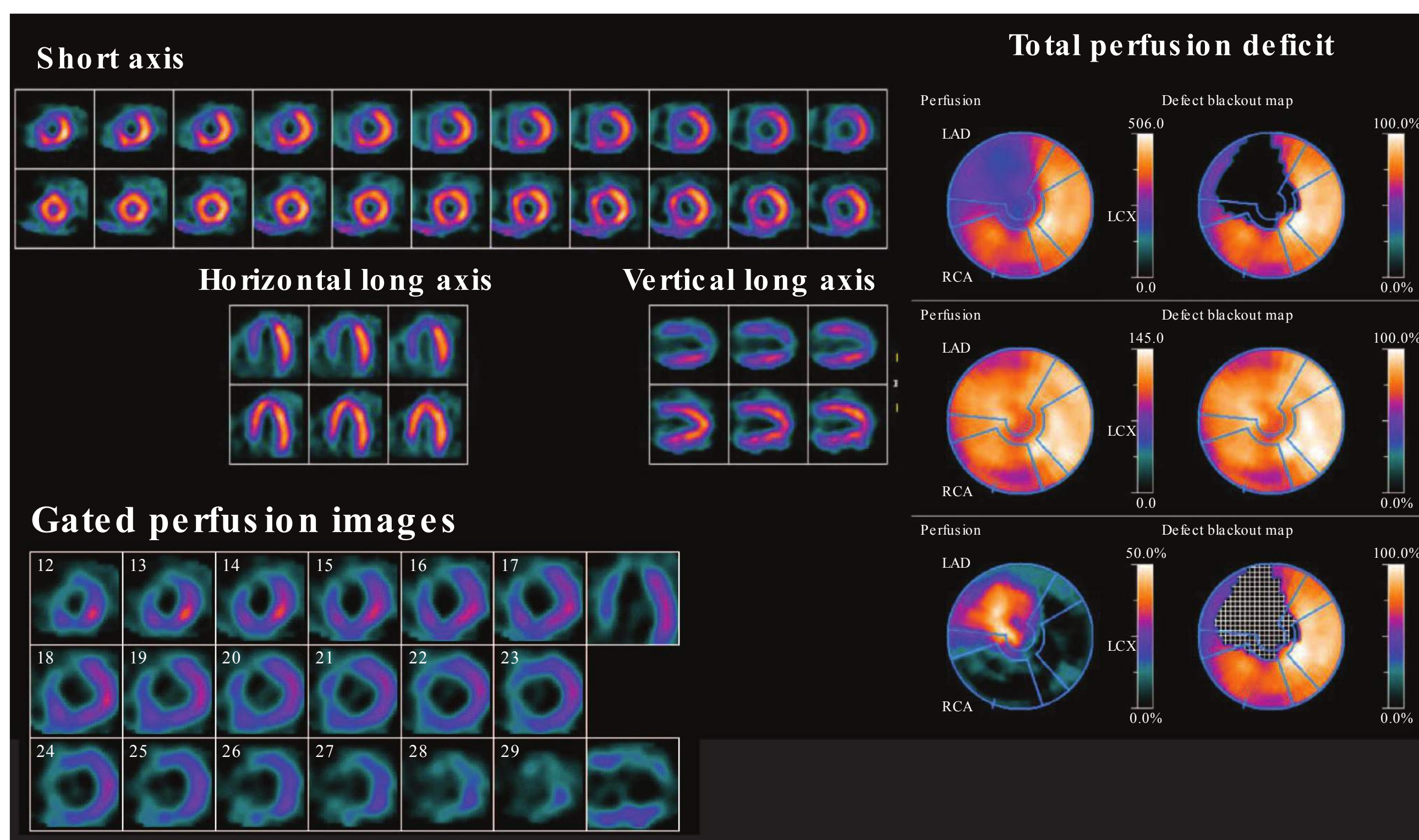


FIGURE 12-5

Tomographic stress (top of each pair) and rest myocardial perfusion images with technetium-99m sestamibi single-photon emission computed tomography imaging demonstrating a large perfusion defect throughout the anterior and anteroseptal walls. The right panel demonstrates the quantitative extent of the perfusion

abnormality at stress (top bull's-eye), at rest (middle bull's-eye), and the extent of defect reversibility (lower bull's-eye). The lower left panel demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction.

PET myocardial perfusion imaging is an alternative to SPECT and is associated with improved diagnostic accuracy and lower radiation dose to patients due to the fact that radiotracers are typically short lived (Table 12-1). The ultra-short half-life of some PET radiopharmaceuticals in clinical use (e.g., rubidium-82) is the primary reason why imaging is generally combined with pharmacologic stress, as opposed to exercise, because this allows for faster imaging of these rapidly decaying radiopharmaceuticals. However, exercise is possible for relatively longer lived radiotracers (e.g., ¹³N-ammonia). PET imaging protocols are typically faster than SPECT, but more expensive. For myocardial perfusion imaging, rubidium-82 does not require an on-site medical cyclotron (it is available from a strontium-82/rubidium-82 generator) and, thus, is the most commonly

used radiopharmaceutical. ¹³N-ammonia has better flow characteristics (higher myocardial extraction) and imaging properties than rubidium-82, but it does require an on-site medical cyclotron. In comparison to SPECT, PET has improved spatial and contrast resolution and provides absolute measures of myocardial perfusion (in mL/min per gram of tissue), thereby providing the patients' regional and global coronary flow reserve. The latter helps improve diagnostic accuracy and risk stratification, especially in obese patients, women, and higher risk individuals (e.g., diabetes mellitus) (Fig. 12-6). Contemporary PET and SPECT scanners are combined with a CT scanner (so-called hybrid PET/CT and SPECT/CT). CT is used primarily to guide patient positioning in the field of view and for correcting inhomogeneities in radiotracer distribution due to attenuation by soft tissues (so-called attenuation

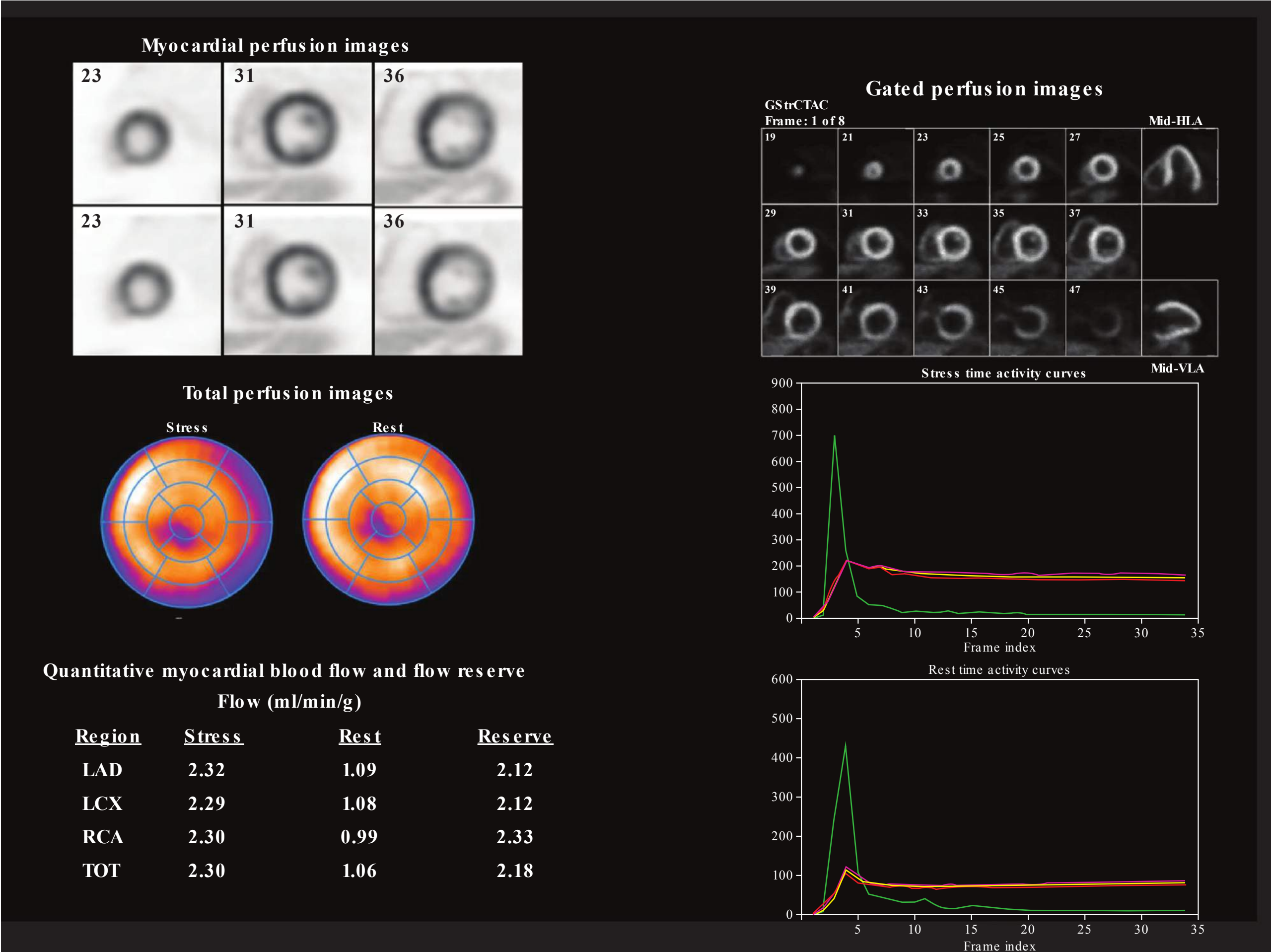


FIGURE 12-6 Multidimensional cardiac imaging protocol with positron emission tomography. The left upper panel demonstrates stress and rest short-axis images of the left and right ventricles demonstrating normal regional myocardial perfusion. The middle panel demonstrates the quantitative bull's-eye display to evaluate the extent and severity of perfusion defects. The lower right panel illustrates the time-activity curves for quantification

of myocardial blood flow. The right upper panel demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TOT, total left ventricle.

correction). However, it can also be used to obtain diagnostic data including coronary artery calcium score and/or CT coronary angiography (discussed below).

For the evaluation of myocardial viability in patients with ischemic cardiomyopathy, myocardial perfusion imaging (with SPECT or PET) is usually combined with metabolic imaging (i.e., fluorodeoxyglucose [FDG] PET). In hospital settings lacking access to PET scanning, thallium-201 SPECT imaging is an excellent alternative.

CARDIAC COMPUTED TOMOGRAPHY

CT acquires images by passing a thin x-ray beam through the body at many angles to generate cross-sectional images. The x-ray transmission measurements are collected by a detector array and digitized into pixels that form an image. The grayscale information in individual pixels is determined by the attenuation of the x-ray beam along its path by tissues of different densities, referenced to the value for water in units known as Hounsfield units. In the resulting CT images, bone appears bright white, air is black, and blood and muscle show varying shades of gray. However, due to the limited contrast between cardiac chambers and vascular structures, iodinated contrast agents are necessary for most cardiovascular indications. Cardiac CT produces tomographic images of the heart and surrounding structures. With modern CT scanners, a three-dimensional dataset of the heart can be acquired in 5–15 s with submillimeter spatial resolution.

CT calcium scoring

CT calcium scoring is the simplest application of cardiac CT and does not require administration of iodinated contrast. The presence of coronary artery calcification

has been associated with increased burden of atherosclerosis and cardiovascular mortality. Coronary calcium is then quantified (e.g., Agatston score) and categorized as minimal (0–10), mild (10–100), moderate (100–400), or severe (>400) (Fig. 12-7). Coronary artery calcium (CAC) scores are then normalized by age and gender and reported as percentile scores. Population-based studies in asymptomatic cohorts have reported high cardiac prognostic value of CT calcium score. With appropriate techniques, the radiation dose associated with CAC scanning is very low (~1–2 mSv).

CT coronary angiography

Coronary CT angiography (CTA) is emerging as a viable alternative to coronary angiography in selected patients. Imaging of the coronary arteries by CT is challenging because of their small luminal size and because of cardiac and respiratory motion. Respiratory motion can be reduced by breath-holding, and cardiac motion is best reduced by slowing the patient's heart rate, ideally to under 60 beats/min, using intravenous or oral beta blockade or other rate-lowering drugs. When performing a coronary CTA, image quality is further enhanced using sublingual nitroglycerin to enlarge the coronary lumen just prior to contrast injection. Imaging the whole-heart volume is synchronized to the administration of weight-based and appropriately timed intravenous iodinated contrast. Image acquisition is linked to the timing of the cardiac cycle through electrocardiogram (ECG) triggering. Prospective ECG triggering, whereby the x-ray beam is turned on during a specific part of the cardiac cycle (e.g., end systole, combined end-systolic and end-diastolic timing, or mid-diastole), is generally used to limit the radiation exposure to the patient by acquiring data only through that portion of

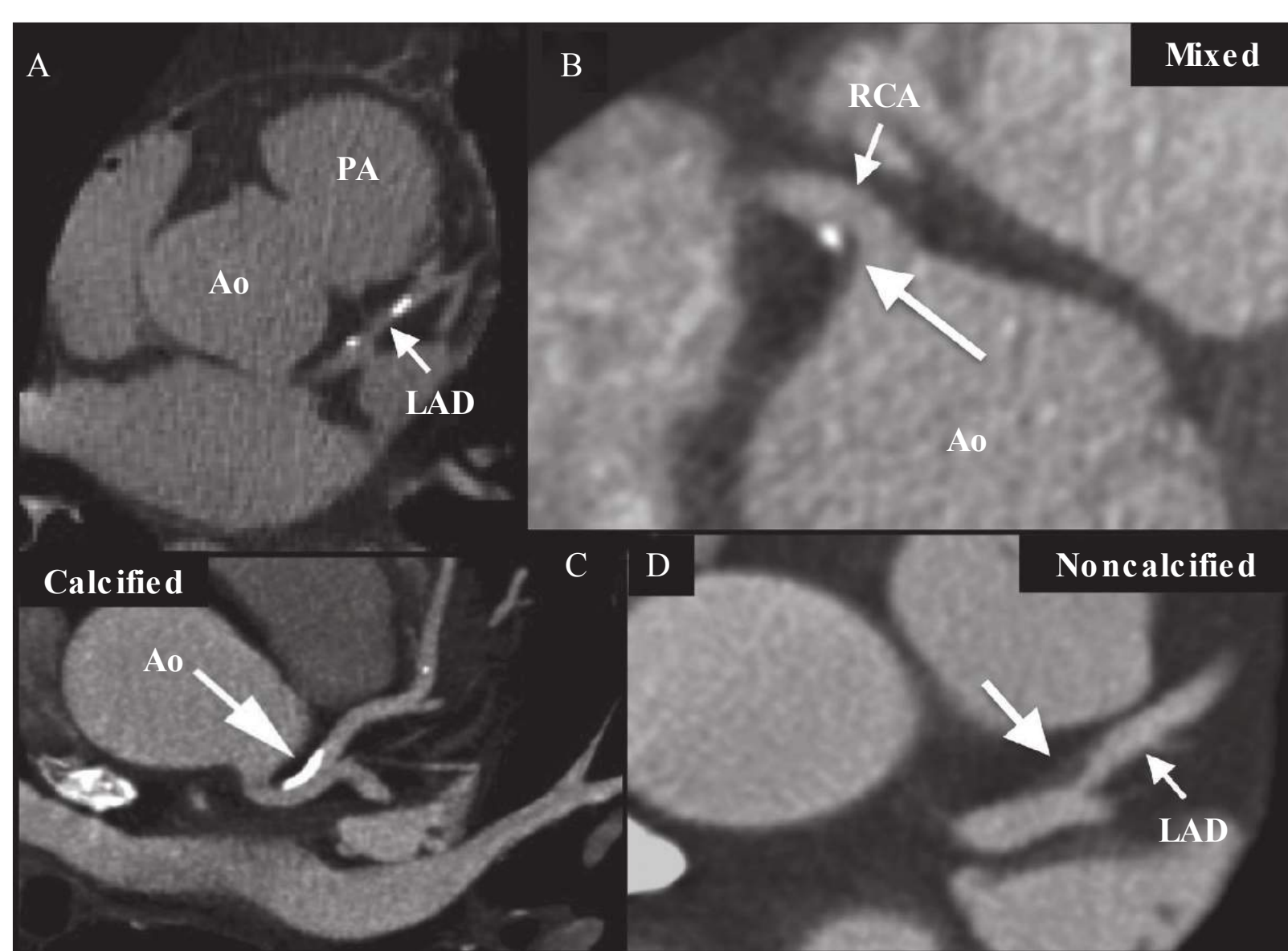


FIGURE 12-7

Examples of non-contrast- and contrast-enhanced coronary imaging with computed tomography (CT). A. Calcified coronary plaques in the distal left main and proximal left anterior descending coronary artery (LAD) in a noncontrast cardiac CT scan. Calcium deposits are dense and present as bright white structures on CT, even without contrast enhancement. B, C, and D. Different types of atherosclerotic plaques on contrast-enhanced CT scans. Importantly, noncalcified plaques are evident only on contrast-enhanced CT scans. AO, aorta; PA, pulmonary artery; RCA, right coronary artery.

112 the cardiac cycle with least motion. Dose modulation is another method that should be routinely used to reduce radiation when performing CTA. It delivers a maximal amount of x-ray during the portion of the cardiac cycle of interest, but reduces x-ray delivery throughout the remaining portion of the cardiac cycle. The resulting images are then postprocessed using a three-dimensional workstation, which facilitates interpretation of the coronary anatomy and estimation of the severity of atherosclerosis (Fig. 12-7).

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) imaging is based on imaging of protons in hydrogen. Hydrogen is abundant because 80% of the human body consists of water. When put inside the MRI scanner, the magnetic field causes the protons (spins) to spin around their axis (a process known as precession) at specific frequencies. Spins within water have a different frequency than spins within more complex macromolecules such as fat or protein. Inside the MRI, a set of gradient coils slightly modifies the magnetic field in each of the three orthogonal directions. As a result, this additional process alters the frequencies of spins, and now the spins can be spatially located inside the MRI bore. This system allows the MRI to selectively deposit radiofrequency energy (in the form of radiofrequency pulse) into specific locations of the body for the purpose of imaging those locations. Once the radiofrequency pulses stop, the energy absorbed by the body will quickly be released back. Using the proper arrangement of surface phased-array coils, this released energy can be read, and important information such as spin locations and frequencies can be digitally recorded in a data matrix known as the K-space, before reconstructed into a magnetic resonance image. Radiofrequency energy deposition into the patient's body can be arranged in many complex ways, known as pulse sequences, that allow extraction of different types of information from the body regions of interests. In CMR, these types of information in general are categorized under T1, T2, or T2* weighting, each of them containing a different combination of diagnostic information regarding cardiac structure, tissue characteristics, blood flow, or other physiologic properties of the heart.

In clinical CMR, most pulse sequences are T1-weighted sequences, which characterize cardiac structure and function, blood flow, and myocardial perfusion, whereas T2-weighted and T2*-weighted pulse sequences characterize myocardial edema and myocardial iron infiltration, respectively. A combination of more than one weighting is possible in some pulse sequences. ECG-triggered cine CMR is the modality that serves as a reference standard for quantifying

TABLE 12-2

CLINICAL CARDIAC MAGNETIC RESONANCE PULSE SEQUENCES AND THEIR APPLICATION	
PULSE SEQUENCE	KEY IMAGING INTERESTS
Cardiac Morphology	
Still frame imaging (black or bright blood)	Cardiac structures
Cardiac Function	
Cine imaging	Left ventricular volume and function
Cine myocardial tagging	Left ventricular deformation (strain)
Blood Flow Imaging	
Velocity-encoded phase contrast	Cardiac and great vessel flow
Stress Testing	
Myocardial perfusion imaging	Regional myocardial blood flow
Cine imaging	Regional wall motion
Myocardial Tissue Characterization	
Late gadolinium enhancement	Myocardial infarction and infiltrative disease
T2-weighted imaging	Myocardial edema
Iron content imaging	Myocardial iron infiltration
Magnetic Resonance Angiography	
Aorta, peripheral and coronary arteries	Luminal stenosis and vessel wall remodeling

ventricular volumes and function. Respiratory motion during CMR imaging is suppressed most commonly using repetitive patient breath-holding, but more advanced algorithms such as motion averaging or gating diaphragmatic motion (known as navigator guidance) are also used in clinical CMR. A list of common pulse sequence used in CMR is shown in [Table 12-2](#).

ASSESSMENT OF CARDIAC STRUCTURE AND FUNCTION

Echocardiography, CMR, and cardiac CT are all capable of assessing cardiac structure and function, although echocardiography is generally considered the primary imaging method for these assessments. Radionuclide imaging can also be used to assess left ventricular regional and global systolic function. Echocardiography is most often used to assess the size of all four chambers and thickness of ventricular walls, which are affected by both cardiac and systemic diseases.

The structure of the left ventricle is generally assessed by determining its volume and mass. Left ventricular volumes can be easily estimated from two-dimensional echocardiography by using one of several validated methods. The accuracy of these methods by echocardiography is limited by the fact that, as a nontomographic technique, foreshortening of the imaging plane can lead to underestimation of volumes. Moreover, virtually all of these methods require accurate identification of the endocardial border, which is dependent on image quality. In this regard, high-resolution tomographic techniques such as CMR or cardiac CT are considered generally more accurate for volumetric assessment. Three-dimensional echocardiography has several advantages over two-dimensional echocardiography by not requiring any geometric assumptions about the left ventricle for quantification of volumes and ejection fraction. However, acquisition of three-dimensional echocardiographic images requires substantial expertise, and these techniques are not widely used in practice.

Left ventricular dilatation is common to a number of cardiac diseases. For example, regional dysfunction secondary to myocardial infarction can ultimately lead to progressive ventricular dilatation or remodeling. Although dilatation often begins in the region affected by the infarction, subsequent compensatory dilatation can occur in remote myocardial regions as well. The presence of regional wall motion abnormalities associated with ventricular thinning (reflecting scar) in a coronary distribution is strongly suggestive of an ischemic etiology. Direct assessment of infarcted myocardium is possible with both CMR (evident as areas of late gadolinium enhancement [LGE]) and radionuclide imaging (as assessed by regional perfusion or metabolic defects at rest). CMR can be particularly useful in determining etiology of ventricular dilatation and dysfunction, with LGE in coronary distributions being nearly pathognomonic for infarction ([Video 12–1](#)).

More global ventricular dilatation is seen in cardiomyopathy and dilatation due to valvular heart disease. Idiopathic, nonischemic cardiomyopathies will typically result in global ventricular dilatation and dysfunction, with thinning of the walls. Patients with substantial ventricular dyssynchrony due to conduction abnormalities will have a typical pattern of contraction (e.g., delay of contraction of the lateral wall with left bundle branch block). Although various methods for determining ventricular dyssynchrony have been proposed as ways to identify patients who would benefit from cardiac resynchronization therapy, it is not yet clear that they are superior to ECG assessment of QRS duration and morphology. As discussed later in this chapter, regurgitant lesions of either the mitral or aortic valves can lead to substantial ventricular dilatation, and assessment of

ventricular size is integral in the evaluation and timing of surgical correction. Because changes in ventricular size are used clinically to determine which patients should undergo valve surgery, accurate assessment of changes in ventricular size is essential. Although serial echocardiography can provide these data, serial assessment by CMR may be more accurate when appreciation of subtle changes over time is important.

Left ventricular wall thickness and mass are also important measures of cardiac and systemic disease. The left ventricle will hypertrophy under any condition in which its afterload is increased, including conditions that obstruct outflow, such as aortic stenosis, hypertrophic cardiomyopathy, and subaortic membranes; in postcardiac aortic obstruction seen in coarctation; or in systemic conditions characterized by increased afterload, such as hypertension. The pattern of ventricular hypertrophy can change depending on the etiology. Aortic stenosis and hypertension are typically characterized by concentric hypertrophy, in which the ventricular walls thicken “concentrically” and cavity size is usually small. In volume overload conditions such as mitral or aortic regurgitation, there may be minimal increase in ventricular wall thickness, but substantial ventricular dilatation leads to marked increases in left ventricular mass.

Ventricular wall thickness can be measured and ventricular mass can be calculated by either echocardiography or CMR. Although radionuclide imaging and cardiac CT can also provide measures of left ventricular mass, they are not generally used for this purpose. Although measurement of wall thickness with echocardiography is relatively straightforward and accurate, determining left ventricular mass by echocardiography requires using one of several formulas that takes into account both wall thickness and ventricular cavity dimensions. Assessment of left ventricular mass by CMR has the advantage of not requiring geometric assumptions and is thus more accurate than echocardiography.

ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC FUNCTION

Assessment of ejection fraction, or the percentage of blood ejected with each beat, has been the primary method to assess systolic function and is generally calculated by subtracting end-systolic volume from end-diastolic volume and dividing by end-diastolic volume. All cardiac imaging modalities can provide direct measurements of left ventricular ejection fraction (LVEF). As discussed above, tomographic techniques (e.g., CMR, CT, and radionuclide imaging [SPECT and PET]) are generally more accurate and reproducible than echocardiography because there are no geometric assumptions. A LVEF of 55% or greater is generally

considered normal, and an LVEF of 50–55% is considered in the low-normal range.

Newer methods to assess systolic function, such as myocardial strain or deformation imaging using speckle-tracking methods on echocardiography or myocardial tagging on CMR, can provide a more sensitive approach to detection of systolic dysfunction. Additional assessments based on these novel methods include assessment of myocardial twist and torsion. Although these techniques are not used routinely, they may be especially useful in certain conditions such as valvular heart disease and early detection of cardiotoxicity following chemotherapy and/or radiation therapy. In addition to estimation or calculation of ejection fraction, stroke volume can be assessed by virtually all cardiac imaging methods, generally by subtracting the end-systolic volume from the end-diastolic volume, or by Doppler methods (only on echocardiography), and offers another measure of systolic function that provides independent information from ejection fraction.

ASSESSMENT OF LEFT VENTRICULAR DIASTOLIC FUNCTION

Echocardiography remains the primary method for clinical assessment of diastolic function. Recent advances in Doppler tissue imaging allow for accurate assessment of the velocity of myocardial wall motion by assessing the excursion of the mitral annulus in diastole. Mitral annular relaxation velocity, or E' , is inversely related to the time constant of relaxation, τ , and has been shown to have prognostic significance. Dividing the standard mitral inflow maximal velocity, E , by the mitral annular relaxation velocity yields E/E' , which has been shown to correlate with left ventricular filling pressures. The utility of standard E and A wave ratios for assessment of diastolic function has been questioned. Mitral deceleration time can be a useful measure if very short (<150 ms), suggesting restrictive physiology and severe diastolic dysfunction. Several grading methods for diastolic function have been proposed that take into account a number of diastolic parameters, including Doppler tissue-based relaxation velocities, pulmonary venous Doppler, and left atrial size (**Fig. 12-8**). Diastolic function worsens with aging, and most diastolic parameters need to be adjusted for age.

ASSESSMENT OF RIGHT VENTRICULAR FUNCTION

Right ventricular size and function have been shown to be prognostically important in a variety of conditions. Right ventricular size and function can be assessed by echocardiography, CMR, CT, or radionuclide imaging methods. CMR is considered the most accurate

noninvasive technique to evaluate the structure and right ventricular ejection fraction of the right ventricle (**Video 12-2**). Although first-pass imaging by radionuclide angiography can provide accurate and reproducible measurements of right ventricular volumes and ejection fraction, it is not commonly used. Assessment of the right ventricle by echocardiography has generally been qualitative, owing in part to the unusual geometry of the right ventricle. However, several quantitative methods are available for assessment of right ventricular function, including fractional area change ($FAC = [\text{diastolic area} - \text{systolic area}] / \text{diastolic area}$), which has been shown to correlate with outcomes in heart failure and after myocardial infarction. Excursion of the tricuspid annulus (tricuspid annular plane systolic excursion) is another widely used method to assess right ventricular function, although it is mostly used in research settings.

Abnormalities of right ventricular size and function are generally secondary to either diseases that affect the right ventricle intrinsically or disease in which the right ventricle responds to abnormalities elsewhere in the heart or pulmonary vasculature. Intrinsic diseases that affect the RV include congenital abnormalities, including hypoplastic right ventricle and arrhythmogenic right ventricular dysplasia, and acquired diseases, such as right ventricular infarction and infiltrative diseases that affect the right ventricle. Long-standing pulmonary hypertension or pulmonary outflow tract obstruction leads to right ventricular hypertrophy and ultimately dilatation. Although right ventricular dilatation can occur due to both chronic and acute processes, chronic right ventricular dilatation is usually secondary to long-standing increases in pulmonary pressures and can thus be distinguished from the acute processes that cause right ventricular dilatation. One such acute process that can cause profound right ventricular dilatation and dysfunction is acute pulmonary embolism. In the setting of acute occlusion of a pulmonary artery or branch, an acute rise in pulmonary vascular resistance causes a previously normal right ventricle to dilate and fail due to the increased afterload. In acute pulmonary embolism, right ventricular dilatation and dysfunction are signs of substantial hemodynamic compromise and are associated with a marked increase risk in likelihood of death. In addition to right ventricular dilatation, acute pulmonary embolism is often associated with a specific pattern of regional right ventricular dysfunction, commonly referred to as the McConnell sign, characterized by preservation of right ventricular wall motion in the basal and apical regions and dyskinesis in the region of the mid right ventricular free wall. This abnormality is highly specific for acute pulmonary embolism and is likely secondary to acute increases in right ventricular load.

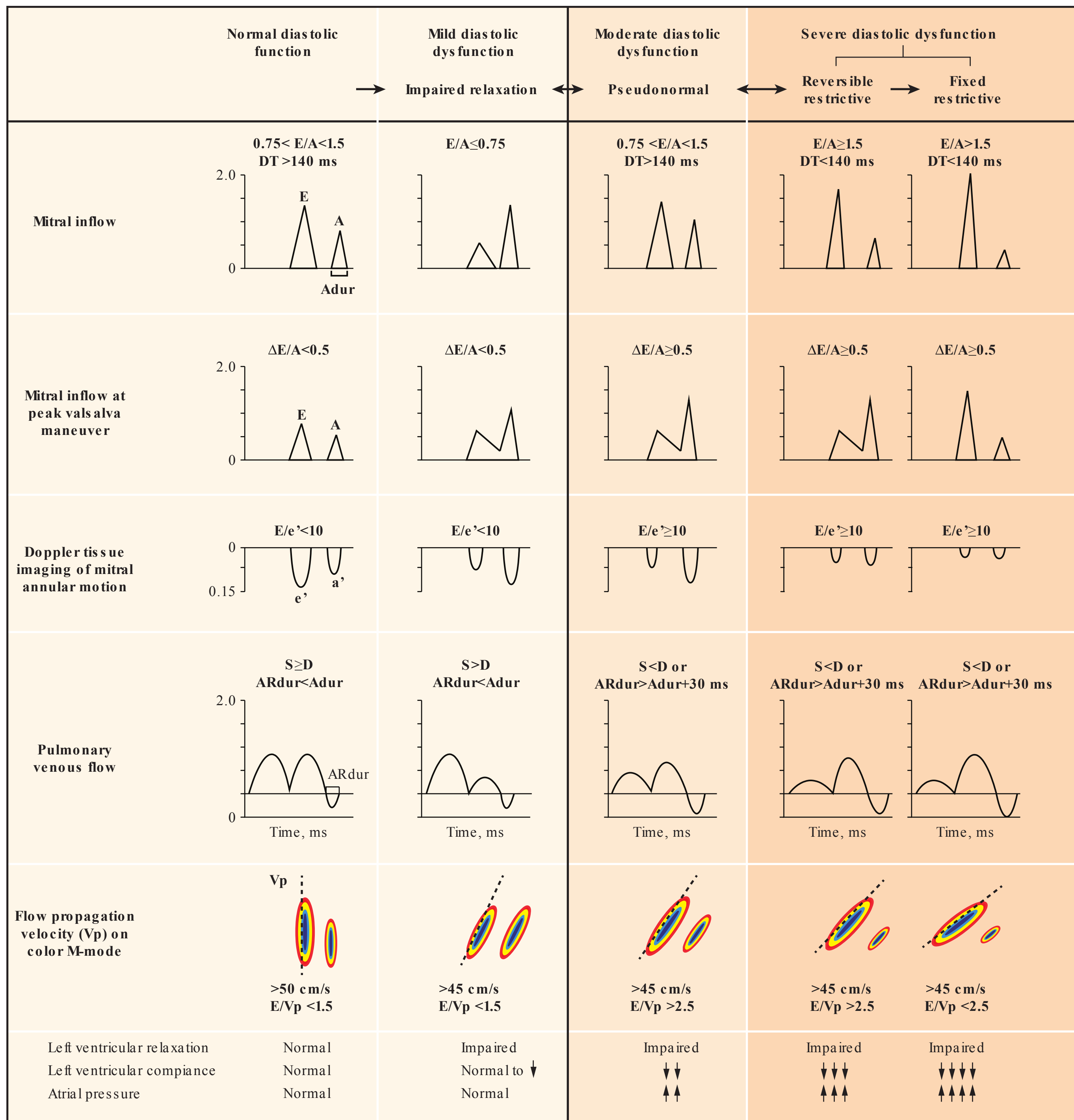


FIGURE 12-8

Stages of diastolic function based on various parameters, including mitral inflow (with and without Valsalva maneuver), Doppler tissue imaging, pulmonary venous flow, and flow

Any disease that causes increased pulmonary vascular resistance can lead to right ventricular dilatation and dysfunction. Long-standing chronic obstructive pulmonary disease results in cor pulmonale in which right ventricular pressures become elevated as the right ventricle hypertrophies in response to the increased pulmonary vascular resistance. Acute pneumonia can

propagation. (Adapted with permission from MM Redfield et al: JAMA 289:194, 2003.)

cause findings that are similar to acute pulmonary embolism. In patients with right ventricular dilatation without obvious pulmonary disease, intracardiac shunts should be considered. The increased flow through the pulmonary vasculature as a result of an atrial septal or ventricular septal defect can, over time, result in elevation in pulmonary resistance with subsequent dilatation

and hypertrophy of the right ventricle. Right ventricular dilatation and dysfunction also have prognostic significance in left-sided heart disease and have been shown to be important predictors of outcome in patients with heart failure or acute myocardial infarction.

In addition to assessment of left ventricular structure, assessment of the other cardiac chambers also provides important clues to intracardiac and systemic diseases. Enlargement of the left atrium is common in patients with hypertension and is also suggestive of increased left ventricular filling pressures; indeed, left atrial size is often termed the “hemoglobin A_{1c} ” of diastolic function, because left atrial enlargement reflects long-standing increase in left-sided filling pressures. Right atrial dilatation and dilatation of the inferior vena cava are common in conditions in which central venous pressure is elevated.

PATIENT SAFETY CONSIDERATIONS

RADIATION EXPOSURE

Both cardiac CT and radionuclide imaging expose patients to ionizing radiation. Several recent publications have raised concern regarding the potential harmful effects of ionizing radiation associated with cardiac imaging. The effective dose is a measure used to estimate the biologic effects of radiation and is expressed in millisieverts (mSv). However, measuring the radiation effective dose associated with diagnostic imaging is complex and imprecise and often results in varying estimates, even among experts. The effective dose from a typical myocardial perfusion SPECT scan ranges between ~4 and 11 mSv, depending on the protocol and type of scanner used. The effective dose from a typical myocardial perfusion PET scan is lower, ~2.5–4 mSv. Radiation exposure associated with cardiac CT is variable and, as with radionuclide imaging, also depends on the imaging protocol and scanner used. Although historic radiation doses with cardiac CT have been quite high, the introduction of newer technologies described above (e.g., x-ray tube modulation, prospective ECG gating) has resulted in a significant dose reduction. The current average radiation dose for a coronary CTA ranges from 5–15 mSv and, in selected cases, can be as low as 1 mSv. Imaging laboratories follow the ALARA (as low as reasonably achievable) principle when balancing the clinical need and imaging approach. By comparison, the average dose for invasive coronary angiography is ~7 mSv, whereas exposure to radiation from natural sources in the United States amounts to ~3 mSv annually.

The risk of a fatal malignancy from medical imaging-related radiation is difficult to estimate precisely but is likely small and difficult to discern from the background risk of natural malignancies. The small but

potential radiation risks from imaging mandate an assessment of the risk-versus-benefit ratio in the individual patient. In this context, one must not fail to take into account the risks of missing important diagnostic information by not performing a test (which could potentially influence near-term management and outcomes) for a theoretical concern of a small long-term risk of malignancy. Before ordering any test, especially one associated with ionizing radiation, we must ensure the appropriateness of the study and that the potential benefits outweigh the risks. The likelihood that the study being considered will affect clinical management of the patient should be addressed before testing is performed. It is also important that “routine” follow-up scans in asymptomatic individuals be avoided.

CONTRAST AGENTS

Contrast agents are commonly used in cardiac CT, CMR, and echocardiography. Although their use significantly enhances the diagnostic information of each of these tests, there are also potential risks from the administration of contrast agents that should be considered.

The risk of adverse reactions from iodinated contrast agents used in cardiac CT is well established. The precise pathogenesis of contrast reactions following intravascular administration of iodinated contrast media is not known. The overall incidence of contrast reactions is 0.4–3% with nonionic formulations and higher for ionic formulations. Most contrast adverse reactions are mild and self-limiting. The risk of contrast-induced nephropathy (CIN) in patients with relatively normal renal function (glomerular filtration rate [GFR] >60 mL/min) is low. In most patients, CIN is self-limited, and renal function usually returns to baseline within 7–10 days, without progressing to chronic renal failure. However, this risk increases in patients with GFR <60 mL/min, especially older diabetic subjects. In such patients, appropriate screening and pre- and post-scan hydration are necessary.

The use of gadolinium-based contrast agents (GBCAs) in CMR imaging enhances the versatility of this technique. Although there are several commercially available GBCAs in the United States, their use in cardiac imaging is considered off-label. Mild reactions from GBCAs occur in ~1% of patients, but severe or anaphylactic reactions are very rare. All GBCAs are chelated to make the compounds nontoxic and to allow renal excretion. Exposure to the nonchelated component of GBCA (Gd^{3+}) has been associated with a rare condition known as nephrogenic systemic fibrosis (NSF), which is an interstitial inflammatory reaction that leads to severe skin induration, contracture of the extremities, fibrosis of internal organs, and even death. Risk factors to developing NSF include high-dose (>0.1 mmol/kg) GBCA use in presence of severe

renal dysfunction (estimated GFR [eGFR] <30 mL/min per 1.73 m²), need for hemodialysis, an eGFR <15 mL/min per 1.73 m², use of gadodiamine contrast agent, acute renal failure, acute systemic illness, and presence of concurrent proinflammatory events. With the use of weight-based dosing and pretest screening, recent data suggest that NSF is extremely rare. Previously, an incidence of 0.02% in 83,121 patients exposed to GBCA over 10 years was noted; however, with current eGFR screening guidelines that have been widely practiced since 2006, a near-zero incidence of NSF has been reported.

Contrast agents can also be used in echocardiography. Injected agitated saline is used routinely to assess cardiac shunts, because these “bubbles” are too large to traverse the pulmonary circulation. After saline injection, the presence of bubbles in the left side of the heart is indicative of shunt, although the location can sometimes be difficult to determine. Dedicated echocardiographic contrast agents have been developed for opacification of left-sided structures and perfusion, although these are only currently U.S. Food and Drug Administration (FDA) approved for perfusion. These agents are either albumin- or lipid-based microspheres filled with inert gases, typically perfluorocarbons. They are considered extremely safe, although they have, in extremely rare instances, been associated with allergic reactions and neurologic events.

SAFETY CONSIDERATIONS OF CMR IN PATIENTS WITH PACEMAKERS AND DEFIBRILLATORS

The risks of performing CMR in the presence of a pacemaker include generation of electrical current from the metallic hardware (especially if wire loops exist), device movement induced by the magnetic field, inappropriate pacing and sensing, and heating as a result of the “antenna’s effect.” While the presence of a permanent pacemaker remains a contraindication to CMR, highly experienced centers had reported success in performing MRI in these patients in a carefully monitored clinical setting. In general, patients need to be not pacemaker-dependent, the setting of the pacemaker needs to be modified to asynchronous mode, and the pulse sequence needs to be modified to reduce the amount of radiofrequency energy deposition. Pacemakers implanted for less than 6 weeks and the presence of epicardial, abandoned, or non-fixation leads are considered unsafe. Collectively, evidence from combined reports of >250 patients with pacemaker models manufactured after year 2000 suggests that CMR at 1.5 T or less can be performed without significant risk for the patient and with minor nonpermanent alteration of pacemaker settings and function. Similar safety data exists for automatic implantable cardioverter-defibrillators (AICDs), but

they are based only on small numbers of patients. In 2011, the first CMR-compatible FDA-approved permanent pacemaker became available commercially. Currently, no AICD has achieved FDA clearance for MRI compatibility.

PATIENT-CENTERED APPLICATIONS OF CARDIAC IMAGING

CORONARY ARTERY DISEASE

The basis for the diagnostic application of imaging tests in patients with known or suspected CAD should be viewed in light of the pretest probability of disease as well as the specific characteristics of imaging tests (i.e., sensitivity and specificity). In symptomatic patients, the prevalence or pretest probability of CAD differs based on the type of symptom (typical angina, atypical angina, noncardiac chest pain), as well as on age, gender, and coronary risk factors. In an individual patient, the results of the initial test informs the posttest likelihood of CAD. In patients undergoing sequential testing (e.g., ECG treadmill testing followed by stress imaging), the posttest probability of disease after the first test becomes the pretest likelihood of disease for the second test. Regardless of the sequence, the expectation is that a test will provide sufficient information to confirm or exclude the diagnosis of CAD and that such information will allow accurate risk stratification to be able to guide management decisions.

Table 12-3 summarizes the relative diagnostic accuracies of cardiac imaging modalities for the diagnosis of CAD.

It is important to highlight that the vast majority of studies included in meta-analyses of the diagnostic accuracy of cardiac imaging modalities for the diagnosis of CAD were retrospective, small, single-center studies, comprising predominantly male patients with a high prevalence of CAD (>50 – 60%). Multicenter studies assessing the performance of individual modalities or comparing different modalities have consistently resulted in more modest diagnostic accuracies, tracking more closely with how these tests perform in practice.

Stress echocardiography

The hallmark of myocardial ischemia during stress echocardiography is the development of new regional wall motion abnormalities and reduced systolic wall thickening (**Video 12-3**). Stress echocardiography can be performed in conjunction with exercise or dobutamine stress. Stress echocardiography is best at identifying inducible wall motion abnormalities in previously normally contracting segments. In a patient with wall motion abnormalities at rest, the specificity of stress echocardiography is reduced, and worsening regional

TABLE 12-3

COMPARATIVE DIAGNOSTIC ACCURACY OF CARDIAC IMAGING APPROACHES TO CORONARY ARTERY DISEASE			
IMAGING MODALITY	PUBLISHED DATA	SENSITIVITY	SPECIFICITY
Exercise echocardiography	15 studies (n = 1849 patients)	84%	82%
Dobutamine echocardiography	28 studies (n = 2246 patients)	80%	84%
SPECT MPI	113 studies (n = 11,212 patients)	88%	76%
Myocardial perfusion PET	9 studies (n = 650 patients)	93%	81%
CMR perfusion	37 studies (n = 2841 patients)	91%	81%
CMR wall motion	14 studies (n = 754 patients)	83%	86%
Coronary CTA	18 studies (n = 1286 patients)	99%	89%

Note: In these studies, the diagnosis of coronary artery disease was based on the presence of a >50% or >70% stenosis on invasive coronary angiography. Abbreviations: CMR, cardiac magnetic resonance; CTA, computed tomography angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

function of a previously abnormal segment might reflect worsening contractile function in the setting of increased wall stress rather than new evidence of inducible ischemia.

The advantages of stress echocardiography over other stress imaging techniques include its relatively good diagnostic accuracy, widespread availability, no use of ionizing radiation, and relatively low cost. Limitations of stress echocardiography include (1) the technical challenges associated with image acquisition at peak exercise because of exertional hyperpnoea and cardiac excursion, (2) the fact that rapid recovery of wall motion abnormalities can be seen with mild ischemia (especially with one-vessel disease, which limits sensitivity), (3) difficulty detecting residual ischemia within an infarcted territory because of resting wall motion abnormality, (4) high operator dependence for acquisition of echocardiographic data and analysis of images, and (5) the fact that good-quality complete images viewing all myocardial segments occurs in only 85% of patients. Newer techniques including second harmonic imaging and the use of intravenous contrast agents improve image quality, but their effect on diagnostic accuracy has not been well documented. The use of IV contrast agents may also allow assessment of myocardial perfusion, although this is not approved or generally reimbursed, and data concerning the utility of contrast perfusion echocardiography are limited.

As with nuclear perfusion imaging, stress echocardiography is often used for risk stratification in patients with suspected or known CAD. A negative stress echocardiogram is associated with an excellent prognosis, allowing identification of patients at low risk. Conversely, the risk of adverse events increases with the extent and severity of wall motion abnormalities on stress echocardiography.

Stress radionuclide imaging

SPECT myocardial perfusion imaging is the most common form of stress imaging tests for CAD evaluation. The presence of a reversible myocardial perfusion defect is indicative of ischemia (Fig. 12-9, left panel), whereas a fixed perfusion defect generally reflects prior myocardial infarction (Fig. 12-9, right panel). As discussed above, PET has advantages compared to SPECT, but it is not widely available and is more expensive and, thus, considered an emerging technology in clinical practice.

Nuclear perfusion imaging is another robust approach to diagnose obstructive CAD, quantify the magnitude of inducible myocardial ischemia, assess the extent of tissue viability, and guide therapeutic management (i.e., selection of patients for revascularization). One of the most valuable clinical applications of radionuclide perfusion imaging is for risk stratification. It is well established that patients with a normal SPECT or PET study exhibit a median rate of major adverse cardiac events of <1% annually. Importantly, the risks of death and myocardial infarction increase linearly with increasing magnitude of perfusion abnormalities, reflecting the extent and severity of CAD.

Despite the widespread use and clinical acceptance of radionuclide imaging in CAD evaluation, a recognized limitation of this approach is that it often uncovers only coronary territories supplied by the most severe stenoses. Consequently, it is relatively insensitive to accurately delineate the extent of obstructive angiographic CAD, especially in the setting of multivessel disease. The use of quantitative myocardial blood flow and coronary flow reserve with PET can help mitigate this limitation. In patients with so-called “balanced” ischemia or diffuse CAD, measurements of coronary flow reserve uncover areas of myocardium at risk that would generally be missed by performing only relative assessments of myocardial perfusion (Fig. 12-10). Conversely, a

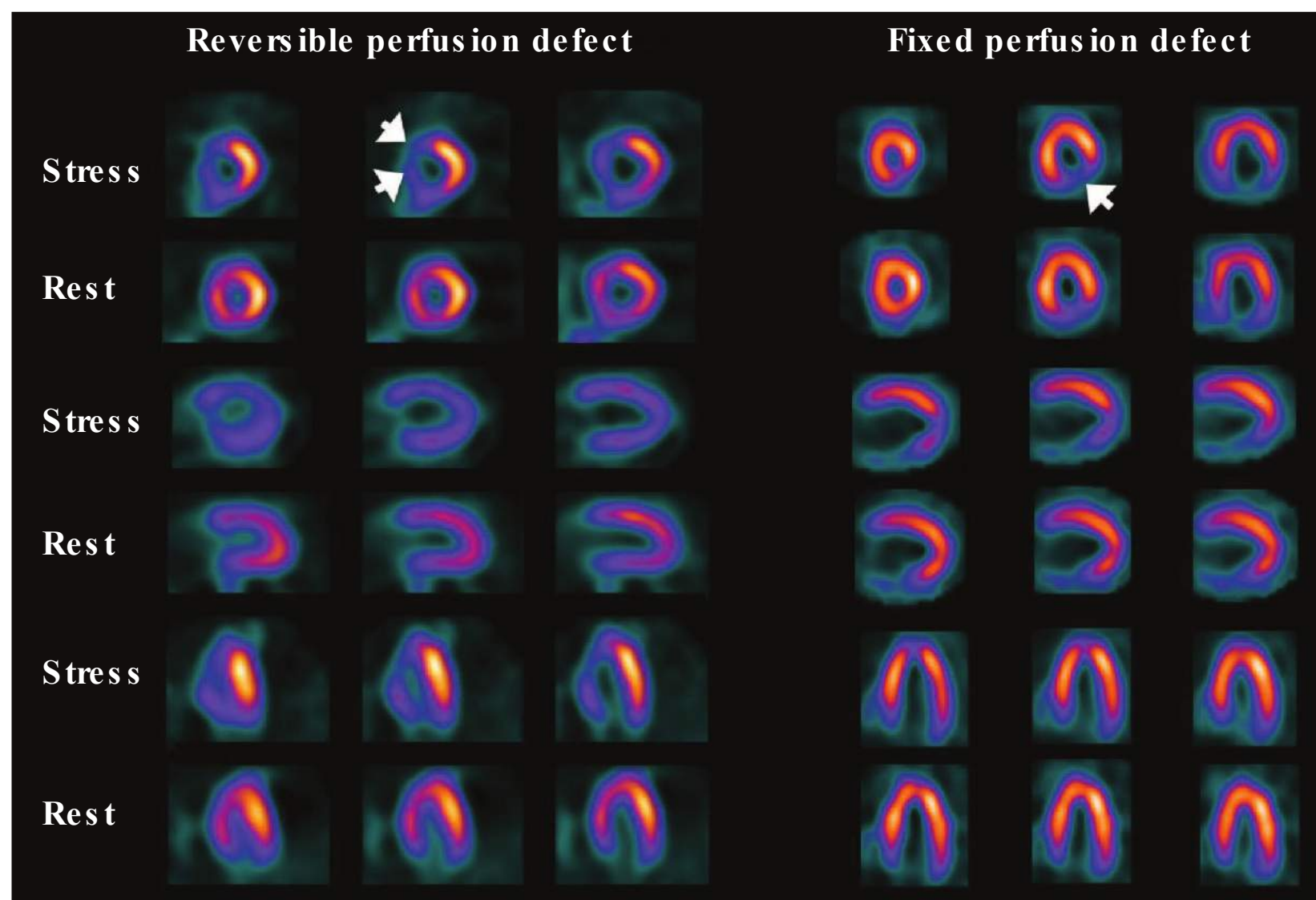


FIGURE 12-9

Selected technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography images of two different patients demonstrating a reversible perfusion defect involving the anterior and septal left ventricular wall, reflecting ischemia in the left anterior descending coronary territory (arrows in left panel), and a fixed perfusion defect involving the inferior and inferolateral walls consistent with myocardial scar in the right coronary territory (arrow in right panel).

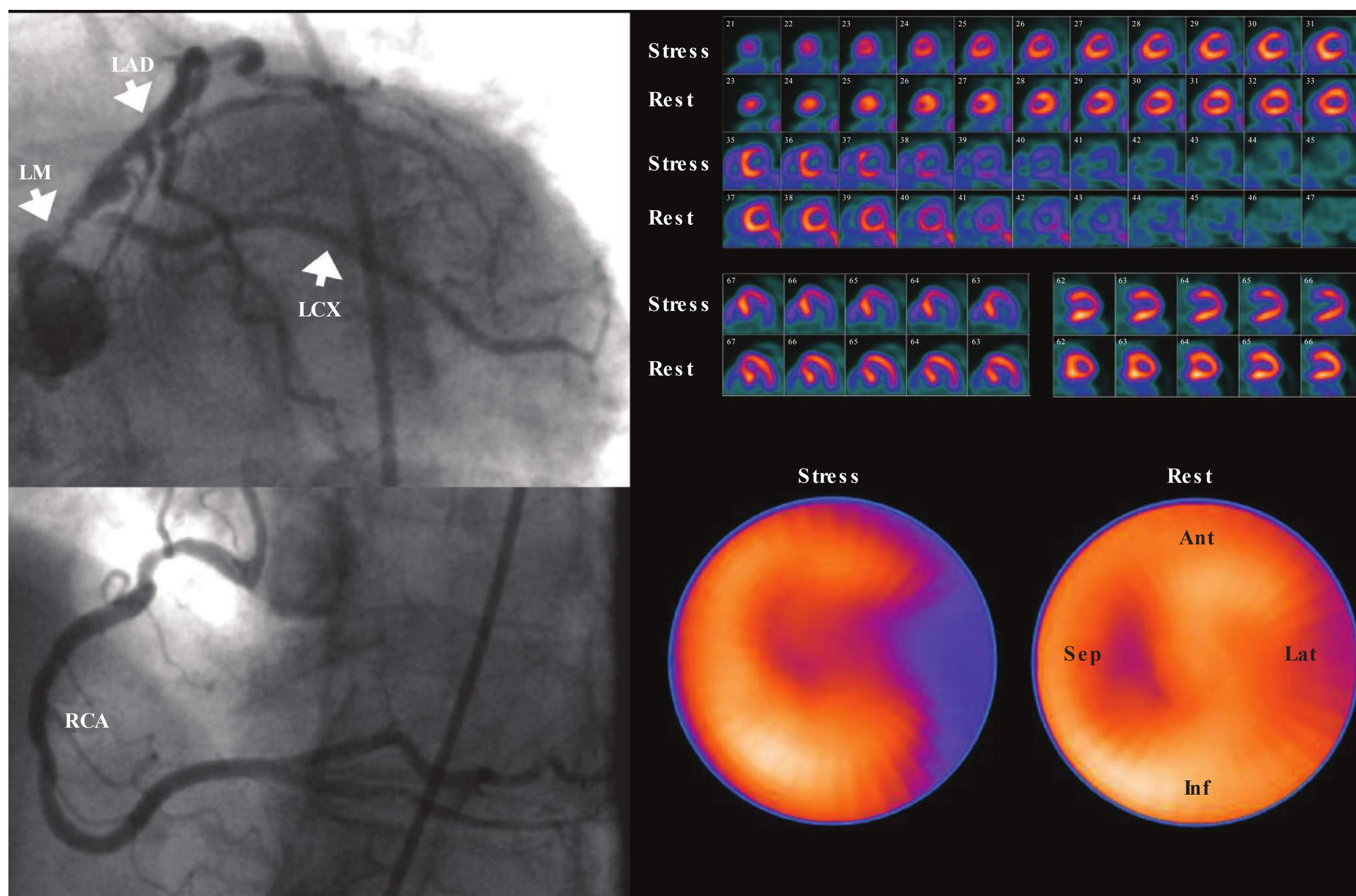


FIGURE 12-10

Coronary angiographic (left panel) and rubidium-82 myocardial perfusion positron emission tomograph images (right panel) in an 85-year-old female with diabetes presenting with chest pain. The coronary angiogram demonstrates significant stenoses of the left main and circumflex coronary arteries. However, the perfusion images demonstrate only a reversible lateral wall defect. Quantification of stress and rest

myocardial blood flow demonstrated a significant, global reduction on coronary flow reserve (estimated at 1.2, normal value >2.0), reflecting extensive myocardium risk that was underestimated by the semiquantitative estimates of myocardial perfusion. LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; RCA, right coronary artery.

normal coronary flow reserve is associated with a very high negative predictive value for excluding high-risk angiographic CAD. These measurements of coronary flow reserve also contribute to risk stratification across the spectrum of ischemic changes, including patients with visually normal myocardial perfusion.

Hybrid CT and nuclear perfusion imaging

Because many of the newer generation nuclear medicine scanners integrate CT and a gamma camera in the same acquisition gantry, it is now possible to acquire and quantify myocardial scar and ischemia and CAC scoring from a single dual-modality study (SPECT/CT or PET/CT) (Fig. 12-11). The rationale for this integrated approach is predicated on the fact that the perfusion imaging approach is designed to uncover only obstructive atherosclerosis. Conversely, CAC scoring (or CT coronary angiography) provides a quantitative measure of the anatomic extent of atherosclerosis. This provides an opportunity to improve the conventional models for risk assessment using nuclear imaging alone, especially in patients without known CAD.

Cardiac CT

Voluminous plaques are more prone to calcification, and stenotic lesions frequently contain large amounts of calcium. Indeed, there is evidence that high CAC scores are generally predictive of a higher likelihood of obstructive CAD, and the available data support the concept of a threshold phenomenon governing this

relationship (i.e., Agatston score >400). However, given the fact that CAC scores are not specific markers of obstructive CAD, one should be cautious in using this information as the basis for referral of patients to coronary angiography, especially in symptomatic patients with low-risk stress tests. Conversely, CAC scores <400 , especially in symptomatic patients with intermediate-high likelihood of CAD, as in those with typical angina, may be less effective in excluding CAD, especially in young symptomatic men and women who may have primarily noncalcified atherosclerosis (Fig. 12-12).

As discussed above, the improved temporal and spatial resolution of modern multidetector CT scanners offer a unique noninvasive approach to delineate the extent and severity of coronary atherosclerosis. The extremely high sensitivity of this approach offers a very effective means for excluding the presence of CAD (high negative predictive value) (Table 12-3). In the setting of high coronary calcium scores (e.g., >400), however, specificity is reduced because the blooming artifact of calcium does not allow one to evaluate the vessel lumen accurately. Given the high negative predictive value of CTA, a normal scan result effectively excludes obstructive CAD and abolishes the need for further investigation. As discussed below, this may be quite useful in patients with low-intermediate clinical risk presenting to the emergency room for chest pain. However, the limited capability of this technique to determine the severity of stenosis and to predict which obstructions are flow limiting can make abnormal scan

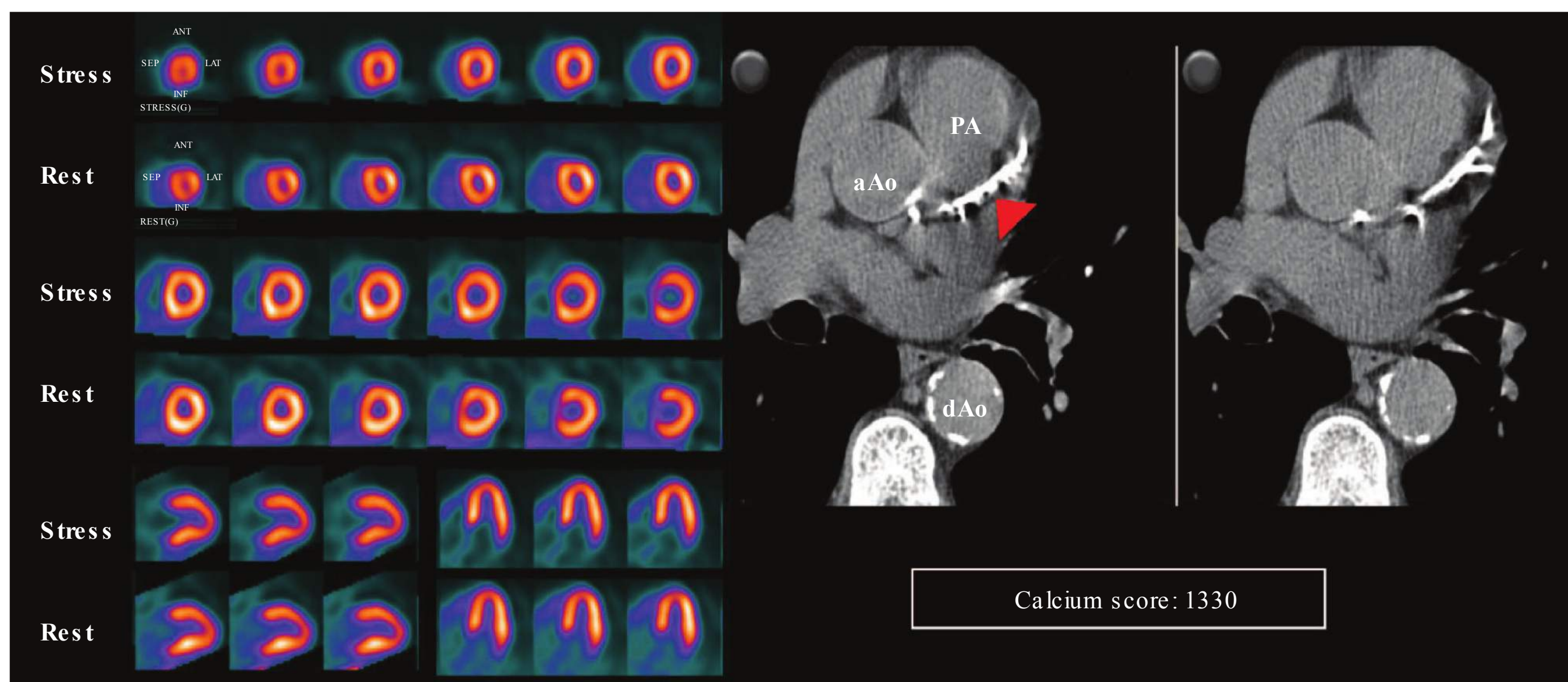


FIGURE 12-11

Stress and rest rubidium-82 myocardial perfusion positron emission tomography (PET) images (left) and non-contrast gated computed tomography (CT) images (right) delineating the extent and severity of coronary artery calcifications obtained with integrated PET/CT imaging. The

images demonstrate extensive atherosclerosis (Agatston coronary calcium score = 1330) without flow-limiting disease based on the normal perfusion study. aAo, ascending aorta; dAo, descending aorta; PA, pulmonary artery.

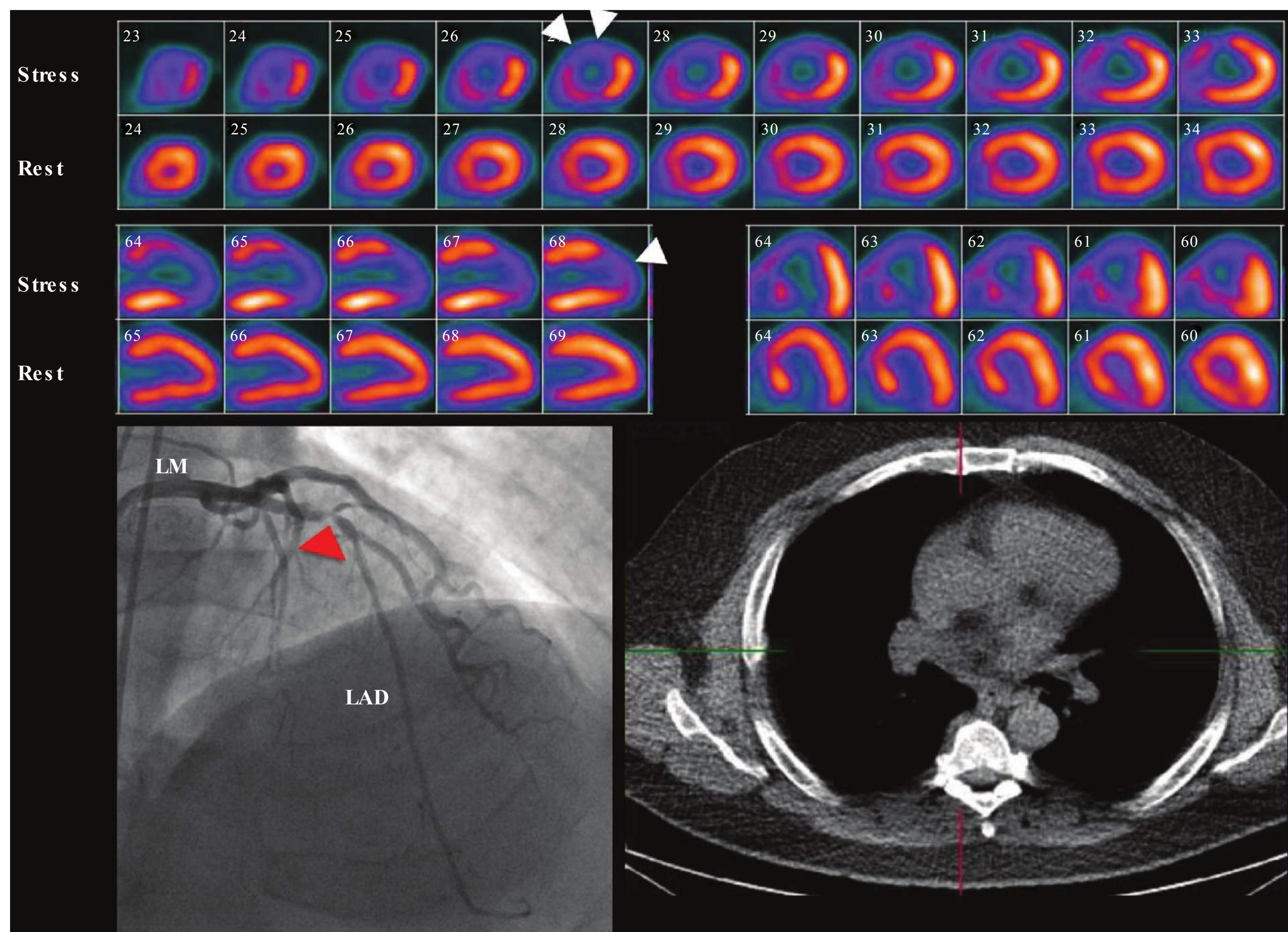


FIGURE 12-12

Stress and rest rubidium-82 myocardial perfusion positron emission tomography images (top), noncontrast gated computed tomography images (lower right), and selected coronary angiographic images obtained on a 59-year-old male patient with atypical angina. Despite the absence of significant coronary calcifications (Agatston calcium score = 0),

the perfusion images demonstrated a dense and reversible perfusion defect involving the anterior and anteroseptal walls (arrows), reflecting significant obstructive disease in the left anterior descending coronary artery (LAD), confirmed on angiography. LM, left main artery.

results more difficult to interpret, especially in terms of the possible need of coronary revascularization. There are emerging data suggesting that by adding a stress myocardial perfusion CT evaluation (similar to stress perfusion CMR) (Fig. 12-13, top panel) or an estimated fractional flow reserve (so-called FFR_{CT}) (Fig. 12-13, lower panel), one can define the hemodynamic significance of anatomic stenosis. However, these are not in routine clinical use and remain emerging technologies.

As with invasive coronary angiography, assessments of the extent of CAD by CTA can also provide useful prognostic information. A low 1-year cardiac event rate has been reported for patients without obstructive CAD on CTA. For patients with obstructive CAD, the risk of adverse cardiac events increases proportionally with the extent of angiographically obstructive CAD.

Although CTA can be helpful in assessing patency of bypass grafts, the assessment of stents is somewhat more challenging because the limited spatial resolution

of CT and stent diameter (<3 mm being associated with the highest number of partial lumen visualization and nondiagnostic scans) both contribute to limited clinical results.

CMR imaging

The two approaches used with CMR to evaluate known or suspected CAD include the assessment of regional myocardial perfusion or wall motion at rest and during stress, the latter being analogous to dobutamine echocardiography. Although treadmill or bicycle exercise stress CMR is practiced in a small number of specialized centers, the logistics for stress MRI studies currently require the use of pharmacologic stress agents including vasodilators or dobutamine. Myocardial perfusion is evaluated by injecting a bolus of a GBCA followed by continuous data acquisition as the contrast passes through the cardiac chambers and into the

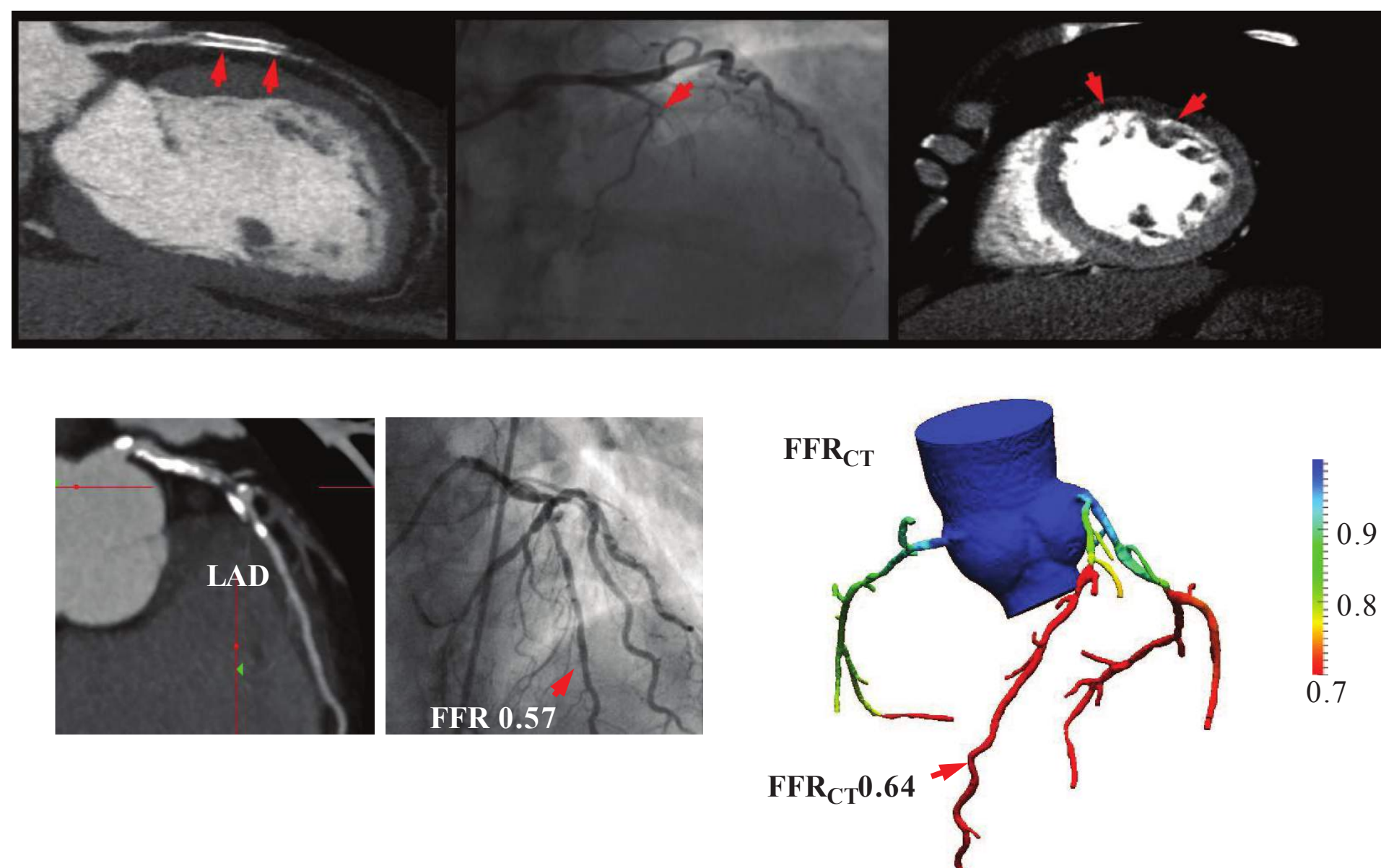


FIGURE 12-13

Examples of novel approaches to the assessment of flow-limiting coronary artery disease (CAD) with cardiac computed tomography (CT). In the top panel, representative views of a coronary CT angiogram (CTA; left), coronary angiogram (middle), and stress myocardial perfusion CT (right) images in a patient with CAD and prior stenting of the left anterior descending coronary artery (LAD) are presented. On the CTA, the stent (arrows) is totally occluded as evidenced by the loss of contrast enhancement distal to the stent. The coronary angiogram demonstrates a concordant total occlusion of the LAD. On the perfusion CT images, there is a black rim (arrows) involving the anterior

and anterolateral walls, indicating the lack of contrast opacification during stress consistent with myocardial ischemia. (Images courtesy of CORE 320 investigators.) The lower panel illustrates an example of fractional flow reserve (FFR) estimates with coronary CTA (left) compared to the reference standard of invasive FFR. The FFR reflects the pressure differential between a coronary segment distal to a stenosis and the aorta. In normal coronary arteries, there is no gradient, and FFR is 1. An FFR < 0.80 is consistent with a hemodynamically significant stenosis. (Images courtesy of Dr. James Min, Cornell University, New York.)

myocardium. Relative perfusion deficits are recognized as regions of low signal intensity (black) within the myocardium (**Video 12-4**). In addition, LGE imaging allows detection of bright areas of myocardial scar (white), which further enhances the utility of this approach for diagnosis of CAD (**Fig. 12-14**).

The major advantage of dobutamine CMR over dobutamine echocardiography is better image quality and sharper definition of endocardial borders from the blood pool. Consequently, dobutamine CMR appears to have better diagnostic accuracy than dobutamine echocardiography for detection of CAD, especially in patients with poor acoustic window (Table 12-3). A limitation of high-dose dobutamine stress CMR is that it bears the potential risk of severe side effects, such as hypotension and severe ventricular arrhythmias in the inhospitable environment of the magnetic resonance scanner. It occurs rarely (~5%), and most cases can be prevented with proper monitoring of vital signs and regional cine function. The advantage of stress perfusion CMR over SPECT is its clearly higher spatial resolution, allowing

detection of subendocardial defects that may be missed by SPECT. The addition of the information from LGE imaging allows differentiation of hypoperfused (potentially ischemic) from infarcted myocardium and characterizes the extent of myocardial ischemia.

As with other imaging modalities, there is evidence that ischemia measurements derived from stress CMR studies also have prognostic value. In line with the nuclear and echocardiography literature, a normal CMR study is associated with a good prognosis. Conversely, the presence of new wall motion abnormalities, regional perfusion defects, the combination of wall motion abnormalities and perfusion defects, and the presence of LGE are all predictors of adverse events.

Selecting a testing strategy in patients without known CAD

As discussed above, there are many options for the evaluation of a patient with suspected CAD presenting with chest pain symptoms. The critical questions to be

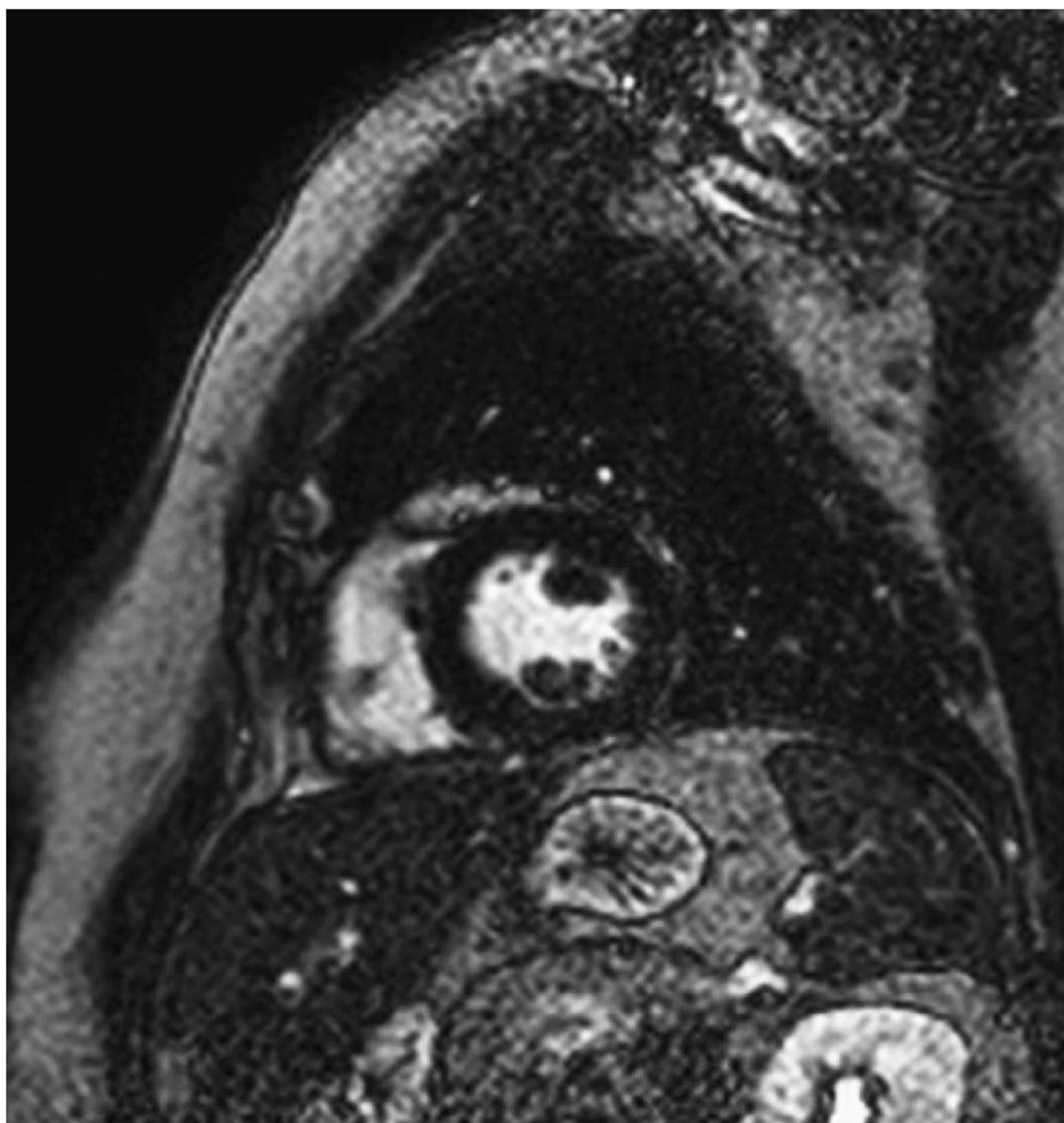


FIGURE 12-14

The image shows the late gadolinium enhancement image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

answered by a testing strategy include the following: (1) Does the chest pain reflect obstructive CAD? (2) What are the short- and long-term risks? (3) Does the patient need to be considered for revascularization?

For symptomatic patients without a prior history of CAD and a normal or nearly normal resting ECG who are able to exercise, the American College of Cardiology/American Heart Association guidelines recommend standard exercise treadmill testing (ETT) as the initial testing strategy. The guidelines further suggest that patients who are categorized as low risk by ETT (e.g., those achieving >10 metabolic equivalents [METs] without chest pain or ECG changes) be treated initially with medical therapy, and those with high-risk ETT findings (i.e., typical angina with >2 mm ST-segment depression in multiple leads, ST elevation during exercise, drop in blood pressure, or sustained ventricular arrhythmias) be referred for coronary angiography.

The use of exercise testing in women presents difficulties that are not seen in men, reflecting the differences in the lower prevalence of obstructive CAD in women and the different accuracy of exercise testing in men and women. Compared with men, the lower pre-test probability of disease in women means that more

test results are false positive. In some of these patients, a positive ETT may reflect true myocardial ischemia caused by microvascular coronary artery dysfunction (so-called microvascular disease). In addition, the inability of many women to exercise to maximum aerobic capacity, the greater prevalence of mitral valve prolapse and microvascular disease in women, and possibly other reasons may contribute to the differences with men as well. The difficulties of using exercise testing for diagnosing obstructive CAD in women have led to speculation that stress imaging may be preferred over standard stress testing. However, recent data from the WOMEN study suggests that in symptomatic, low-risk women who are able to exercise, standard ETT is a very effective initial diagnostic strategy as compared to stress radionuclide imaging. Women included in the study were randomized to standard ETT or exercise radionuclide perfusion imaging. The primary endpoint was the 2-year incidence of major adverse cardiac events, defined as CAD death or hospitalization for an acute coronary syndrome or heart failure. At 2 years, there was no difference in major adverse cardiac events. As expected, ETT resulted in 48% lower costs compared to exercise radionuclide imaging.

Patients with intermediate-high risk after ETT (e.g., low exercise duration, chest pain, and/or ST-segment depression without high-risk features) will often require additional testing, either stress imaging or noninvasive CT coronary angiography, to more accurately characterize clinical risk. Most common stress imaging strategies in intermediate-risk patients include stress echocardiography and radionuclide imaging. In such patients, stress imaging with either SPECT or echocardiography has been shown to accurately reclassify patients who are initially classified as intermediate risk by ETT as low or high risk (Fig. 12-15). Following this staged strategy of applying the low-cost ETT first and reserving more expensive imaging to refine risk stratification to patients initially classified as intermediate risk by ETT is more cost effective than applying stress or anatomic imaging as the initial test routinely.

A stress imaging strategy is the recommended first step for patients who are unable to exercise to an adequate workload and/or those with abnormal resting ECGs (e.g., left ventricular hypertrophy with strain, left bundle branch block). Importantly, the most recent documents regarding appropriate use of radionuclide and echocardiography imaging also considered that an imaging strategy may be an appropriate first step in patients with intermediate-high likelihood of CAD (e.g., diabetics, renal impairment) due to increased overall sensitivity for diagnosis of CAD and improved risk stratification.

In considering the potential clinical application of imaging modalities, the evidence supporting the role of

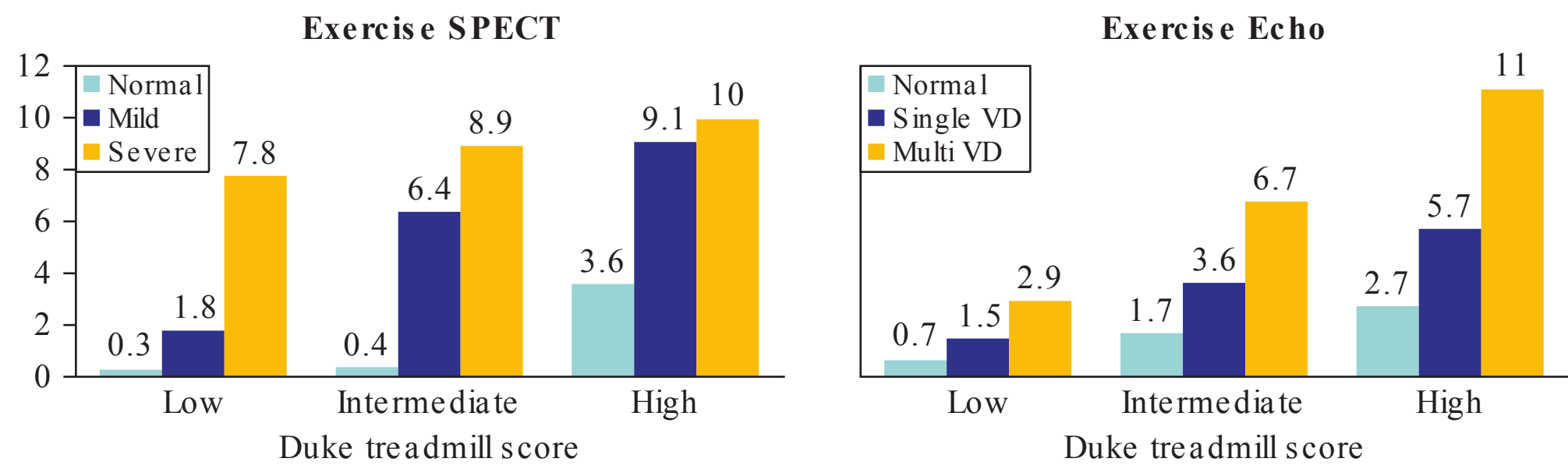


FIGURE 12-15
Incremental risk stratification of stress imaging over Duke treadmill score in patients with suspected coronary artery disease. Stress imaging is most valuable in the intermediate-risk group. SPECT, single-photon emission computed

tomography; VD, vessel disease. (Reproduced with permission from RHachamovitch et al: *Circulation* 93:905, 1996; and TH Marwick et al: *Circulation* 103:2566, 2001.)

assessment of ischemia versus anatomy must be considered. From the discussion above, a normal CTA is helpful because it effectively excludes the presence of obstructive CAD and the need for further testing, defines a low clinical risk, and makes management decisions regarding referral to coronary angiography straightforward. Because of its limited accuracy to define stenosis severity and predict ischemia, however, abnormal CTA results are more problematic to interpret and to use as the basis for defining the potential need of invasive coronary angiography and revascularization. In such patients, a follow-up

stress test is usually required to determine the possible need of revascularization (Fig. 12-16).

The justification of stress imaging in testing strategies has hinged on the identification of which patients may benefit from a revascularization strategy by means of noninvasive estimates of jeopardized myocardium rather than angiography-derived anatomic stenoses. Indeed, there is evidence that only the presence of moderate-severe ischemia identifies patients with apparent improved survival with revascularization. Patients with mild or no ischemia are better candidates for optimal

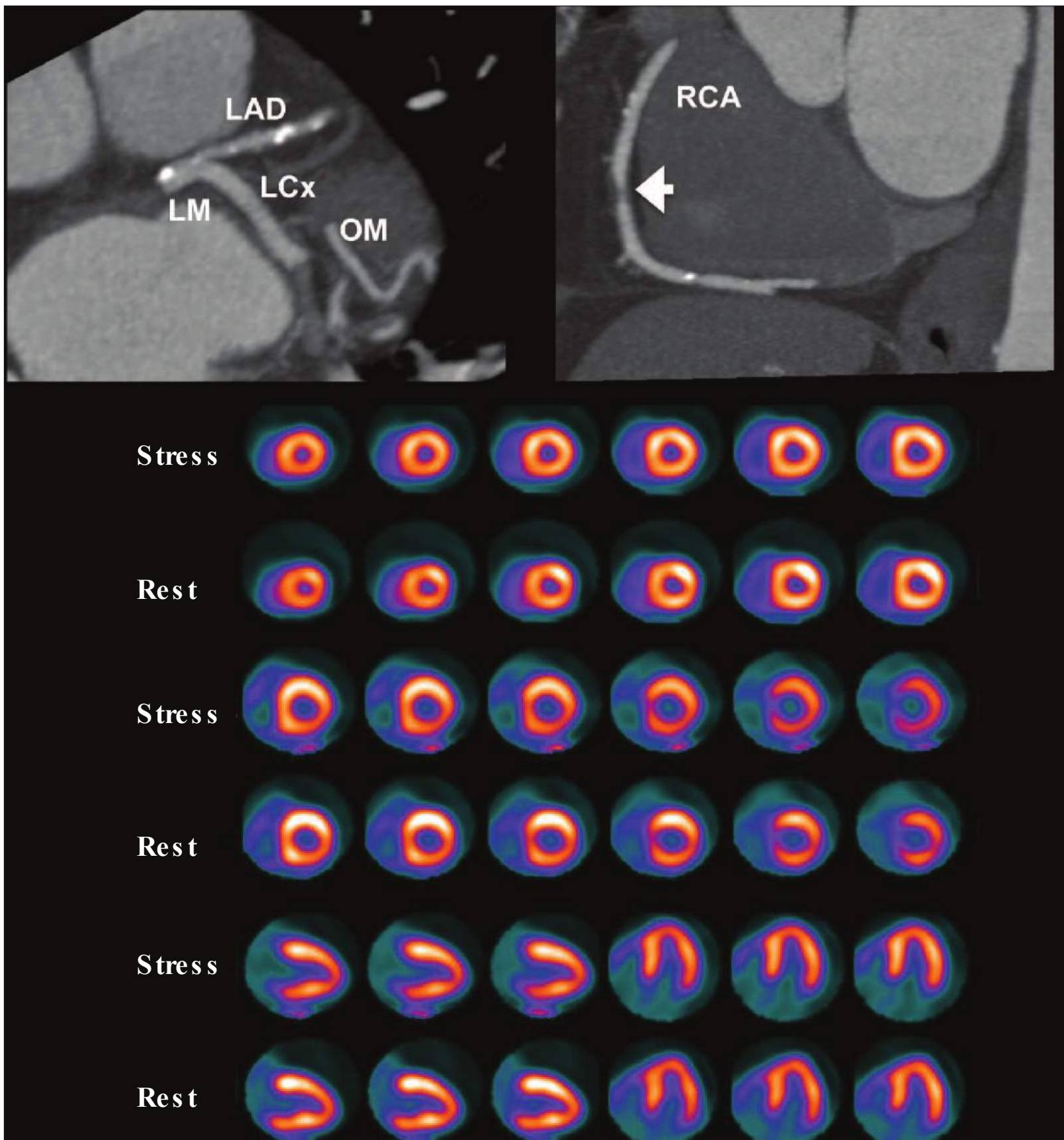


FIGURE 12-16
Selected views from coronary computed tomography angiographic (CTA) images (top panel) and stress and rest rubidium-82 myocardial perfusion positron emission tomography images (lower panel) obtained on a 64-year-old male patient with atypical angina. The CTA images demonstrate dense focal calcifications in the left main (LM) and left anterior descending (LAD) coronary arteries and a significant noncalcified plaque in the mid right coronary artery (RCA; arrow). The myocardial perfusion images demonstrated no evidence of flow-limiting stenosis. LCx, left circumflex artery; OM, obtuse marginal branch.

medical therapy. The advantages of this approach include avoidance of excess catheterizations with their associated cost and risk and the potential for intervening unnecessarily. The acceptable diagnostic accuracy of stress imaging approaches, along with their robust risk stratification, and the ability of ischemia information to identify patients who would benefit from revascularization suggest a potential role as a first imaging strategy in patients with intermediate-high likelihood of CAD. Although the available data suggest similar diagnostic accuracy for SPECT, PET, echocardiography, and CMR, the choice of strategy depends on availability and local expertise.

Selecting a testing strategy in patients with known CAD

Use and selection of testing strategies in symptomatic patients with established CAD (i.e., prior angiography, prior myocardial infarction, prior revascularization) differ from those in patients without prior CAD. Although standard ETT may help distinguish cardiac from noncardiac chest pain, exercise ECG has a number of limitations following myocardial infarction and revascularization (especially coronary artery bypass grafting). These patients frequently have rest ECG abnormalities. In addition, there is a clinical need to document both the magnitude and localization of ischemia to be able to direct therapy, especially the potential need for targeted revascularization. Consequently, imaging tests are preferred for evaluating patients with known CAD.

There are also important differences in the effectiveness of imaging tests in these patients. As discussed above, coronary CTA is limited in patients with prior revascularization. Patients with prior coronary artery bypass grafting are a particularly heterogeneous group with respect to the anatomic basis of ischemia and its implications for subsequent morbidity and mortality. In addition to graft attrition, progression of disease in the native coronary arteries is not uncommon in symptomatic patients. While CTA provides excellent visualization of the bypass grafts, the native circulation tends to get heavily calcified and is generally not a good target for imaging with CTA. Likewise, blooming artifacts from metallic stents also limit the application of coronary CTA in patients with prior percutaneous coronary intervention. Although newer stent material may change the potential role of CTA in the future, it is probably not the first line of testing in these patients. If an anatomic strategy is indicated, direct referral to invasive angiography is preferred.

Stress imaging approaches are especially useful and preferred in symptomatic patients with established CAD. As in patients without prior CAD, normal imaging studies in symptomatic patients with established CAD also identify a low-risk cohort. In those

with abnormal stress imaging studies, the degree of abnormality relates to posttest risk. In addition, stress imaging approaches can localize and quantify the magnitude of ischemia (especially with perfusion imaging), thereby assisting in planning targeted revascularization procedures. As in patients without prior CAD, the choice of stress imaging strategy depends on availability and local expertise.

Testing strategy considerations in patients presenting with chest pain to the emergency department

Although acute chest pain is a frequent reason for patient visits to the emergency department (ED), only a small minority of those presentations represent an acute coronary syndrome (ACS). Strategies used in the evaluation of these patients include novel cardiac biomarkers (e.g., serum troponins), conventional stress testing (ETT), and noninvasive cardiac imaging. It is generally accepted that the primary goal of this evaluation is exclusion of ACS and other serious conditions rather than detection of CAD.

The routine evaluation of acute chest pain in most centers in the United States includes admission to a chest pain unit to rule out ACS with the use of serial ECGs and cardiac biomarkers. In selected patients, stress testing with or without imaging may be used for further risk stratification. Stress echocardiography and radionuclide imaging are among the most frequently used imaging approaches in these patients. The relative strengths and weaknesses of these testing options have been discussed above. Both approaches have been shown to be effective for identifying low-risk patients who can be safely discharged from the ED. Multiparametric CMR imaging has also been used successfully in patients with acute chest pain. In addition to the combined assessment of regional and global left ventricular function, myocardial perfusion, and tissue viability, it is also possible to evaluate the presence of myocardial edema to characterize the myocardium at risk secondary to reduced coronary flow ([Video 12-5](#)). Due to its ability to probe multiple aspects of myocardial physiology, cardiac anatomy, and tissue characterization with LGE imaging, CMR is also useful in diagnosing conditions that mimic ACS (e.g., acute myocarditis, takotsubo cardiomyopathy, pericarditis) ([Fig. 12-17](#)). Thus, CMR imaging offers unique information of myocardial pathophysiology in the spectrum of ACS and is, perhaps, the most versatile of all noninvasive imaging techniques. Unfortunately, it is not widely available even at specialized centers and is not a first-line testing strategy. The main disadvantages of the “functional” testing strategy are that it is time consuming and is generally associated with a prolonged length of stay and, thus, is more costly.

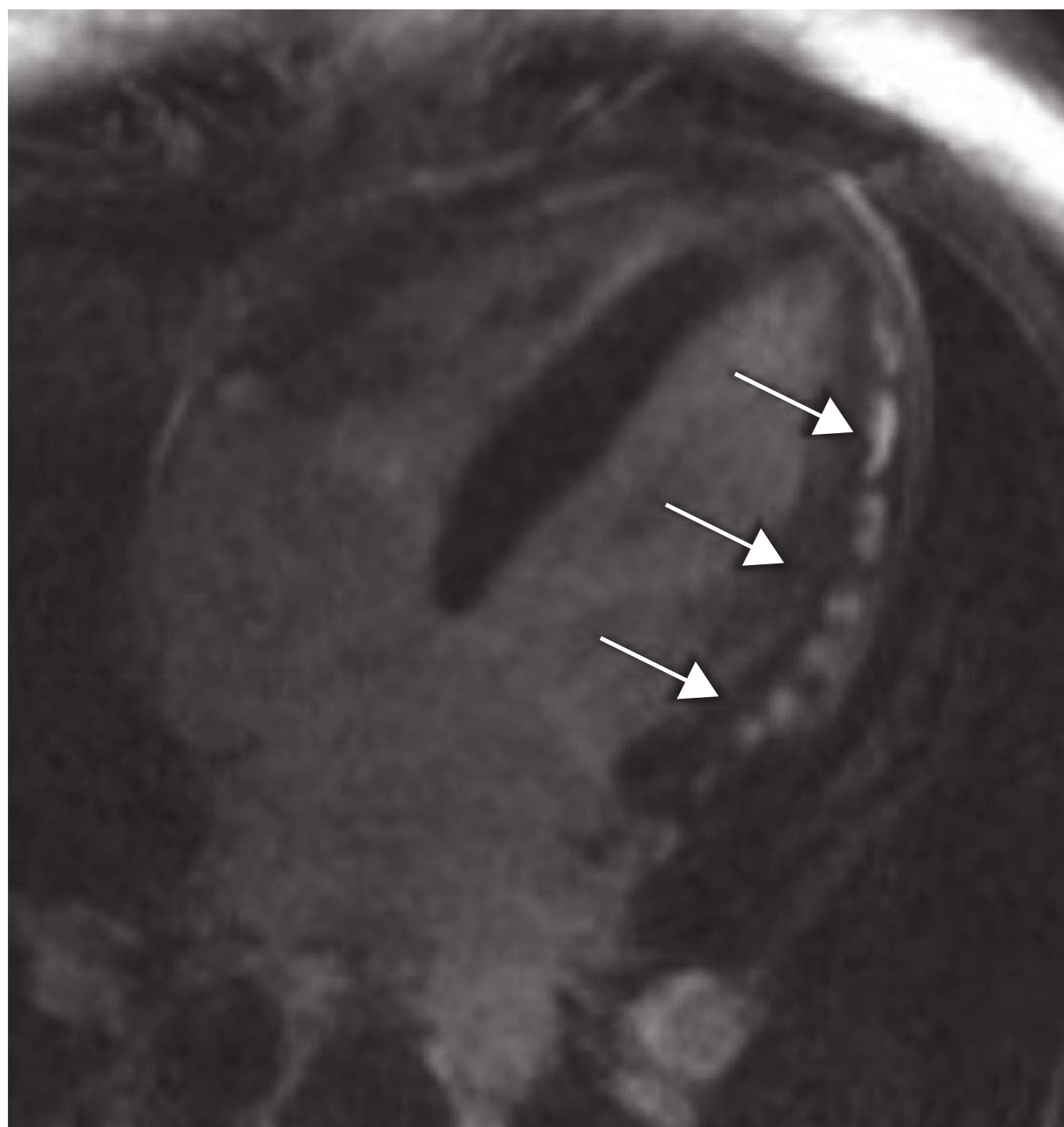


FIGURE 12-17

A four-chamber long-axis late gadolinium enhancement (LGE) image of a patient with acute myocarditis. Note that the LGE primarily involved the epicardial aspect of the myocardium (arrows), sparing the endocardium, which is a feature that distinguishes myocarditis from myocardial infarction, which affects the endocardium. Also note the multiple foci of LGE in this case affecting the lateral wall of the left ventricle. Viral myocarditis often presents with this pattern.

As discussed above, coronary CTA is a rapid and accurate imaging technique to exclude the presence of CAD and is well suited for the evaluation of patients with acute chest pain (**Fig. 12-18**). Several single-center and,

more recently, multicenter studies have demonstrated the feasibility, safety, and accuracy of coronary CTA in the ED. There have been four randomized controlled trials evaluating the efficacy of coronary CTA as the initial testing strategy as compared to usual care (which typically includes stress imaging). Patients in these trials had a very low clinical risk. Overall, there were no deaths and very few myocardial infarctions without differences between the groups. Likewise, there were no differences in postdischarge ED visits or rehospitalizations. These studies showed decreased length of stay with coronary CTA, and most but not all reported cost savings. An observation from a recent meta-analysis was that, compared to usual care, more patients assigned to coronary CTA underwent cardiac catheterization (6.3% vs 8.4%, respectively) and revascularization (2.6% vs 4.6%, respectively). The relative increased frequency in the referral to cardiac catheterization and revascularization after coronary CTA compared to stress imaging testing strategies has also been observed in patients with stable chest pain syndromes.

Taken together, the available data clearly suggest that not all patients presenting with acute chest pain require specialized imaging testing. Patients with very low clinical risk and negative biomarkers (especially high-sensitivity troponin assays) can be safely triaged. The use of imaging tests in patients with low-intermediate risk should be carefully considered, especially given the trade-offs discussed above.

VALVULAR HEART DISEASE

Abnormalities of any of the four valvular structures in the heart can lead to significant cardiac dysfunction, heart failure, or even death. Echocardiography, CMR, and cardiac CT can be used for the evaluation of valvular heart

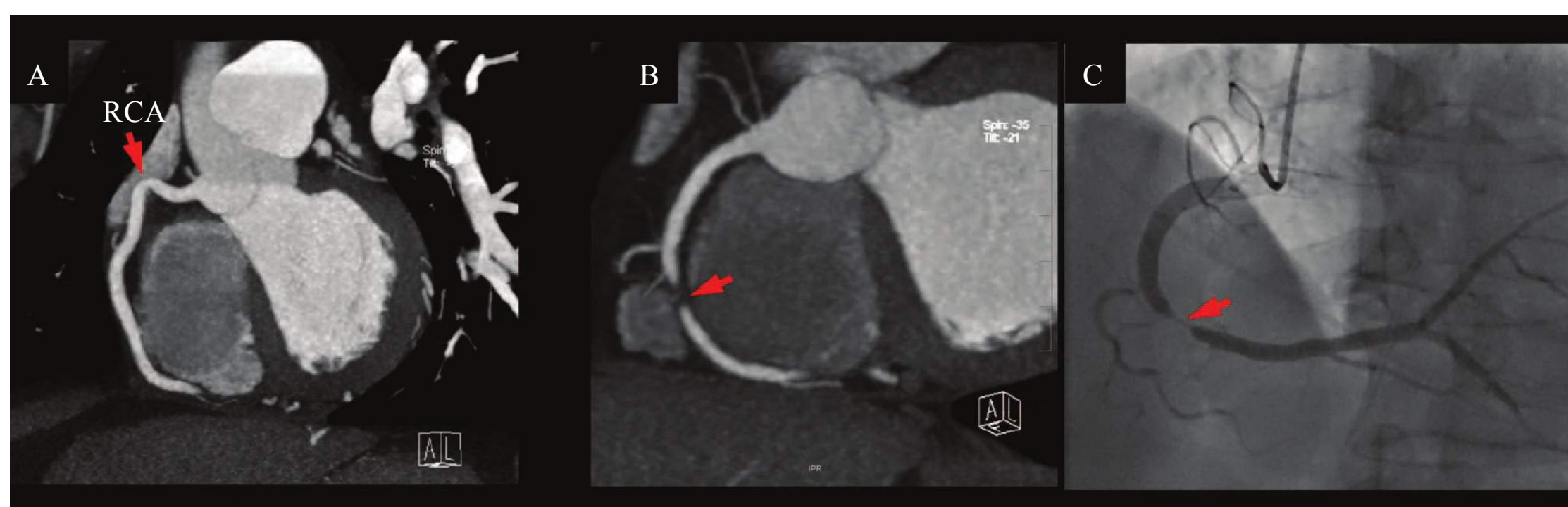


FIGURE 12-18

Representative coronary computed tomography angiographic (CTA) images of two patients presenting to the emergency department with chest pain and negative biomarkers. The patient in A had angiographically normal coronary arteries; the panel shows a representative view of the right

coronary artery (RCA). B and C show a corresponding significant stenosis in the mid portion of the RCA on both the CTA (B) and invasive angiographic view (C). (Images courtesy of Dr. Quynh Truong, Massachusetts General Hospital, Boston, MA)

disease, although echocardiography has generally been considered the first imaging test of choice for the assessment of valvular heart disease. In addition, echocardiography is the most cost-effective screening method for valvular heart disease. In some cases, CMR can complement echocardiography when echocardiographic acoustic window is inadequate, quantifying blood flow data more precisely, or providing complimentary assessment of adjacent vascular structures relevant to the valvular condition.

Echocardiography can be used to assess both regurgitant and stenotic lesions of any of the cardiac valves. Typical indications for echocardiography to assess valvular heart disease include cardiac murmurs identified on physical examination, symptoms of breathlessness that may represent valvular heart disease, syncope or presyncope, and preoperative exams in patients undergoing bypass surgery. A standard echocardiographic examination should include qualitative and quantitative assessment of all valves regardless of indication and should serve as an adequate screening test for significant valvular disease.

General principles of valvular assessment

Direct visualization of valvular structures

Direct visualization of valve structures by two-dimensional echocardiography represents the first step in valvular evaluation. The morphology of valvular structures provides useful information regarding the etiology and severity of valvular disease. For example, two-dimensional imaging assessment of the aortic valve can identify the number of leaflets, determine whether the valve is bicuspid or tricuspid, and determine the severity of calcification and degree of leaflet excursion. Similarly, the classic appearance of a rheumatic mitral valve is extremely useful in determining the etiology of mitral stenosis, and mitral valve prolapse can be instantly identified without even the need for Doppler-based quantification.

Evaluation of stenotic valves

As described earlier in the chapter, evaluation of stenotic valves generally includes estimation of the pressure gradient across the stenosis and determination of the valve area. Both of these measures have diagnostic and prognostic value. For example, when Doppler echocardiography is used to assess the maximal velocity across a stenotic aortic valve, this calculation will provide an accurate measure of the instantaneous gradient across the valve. This gradient will be higher than the mean gradient, as well as higher than that peak-to-peak gradient obtained at cardiac catheterization. This gradient is dependent on both the degree of stenosis and the contractile function of the left ventricle. Patients with significant left ventricular dysfunction may have severe aortic stenosis but will be unable to generate a high

gradient across the valve because generated pressure within the left ventricle will be diminished.

Assessment of stenotic valves generally requires estimation of both the pressure gradient across the valve and the valve area. Pressure gradient is estimated through direct application of the Bernoulli principle, and the formula $p = 4v^2$ is usually sufficient to estimate the gradient across the valve. Several methods can be used to estimate valve areas, including the continuity principle based on the principle of conservation of mass. By this method, flow is estimated in two places. For example, for assessment of the aortic valve area, we measure the flow in the region of the left ventricular outflow tract and the cross-sectional area in this region, the product of which should be equal to the flow across the stenotic aortic valve and its cross-sectional area. Estimation of the mitral valve area in patients with suspected mitral stenosis can also be performed in a number of ways, including planimetry of the valve directly, estimation with continuity methods, or the most commonly used pressure half-time method, in which the stenosis severity is estimated by the time it takes for the pressure—estimated from velocity by the Bernoulli equation—to reach half of its original value during mitral inflow.

Evaluation of regurgitant lesions

Regurgitant lesions are generally assessed by both visual assessment of the valve morphology and a variety of Doppler-based methods to assess the severity of regurgitation. The etiology of regurgitation can often be inferred from visual inspection. For example, prolapse of the mitral valve leaflets—and to a lesser extent, the aortic valve leaflets—can be easily visualized with two-dimensional echocardiography. In general, valvular regurgitation can be caused by abnormalities of the valve leaflets themselves or abnormalities of the annulus and supporting structures, and these can usually be distinguished visually on trans-thoracic echocardiography (see discussion below).

Quantification of valvular regurgitation is more difficult with echocardiography than quantification of valvular stenoses. Doppler-based methods are best suited to assess blood velocities rather than volumetric flow. The most widely used technique for assessing the severity of valvular regurgitation is color flow Doppler estimation, which is qualitative. More quantitative methods such as the proximal isovelocity surface area (PISA) method (see below) allow for more accurate assessment of regurgitation and provide estimation of the regurgitant fraction and effective regurgitant orifice area but are less widely used. Assessment of regurgitant lesions with CMR also has a number of advantages (see below).

Assessment of aortic stenosis

Aortic stenosis, one of the most common forms of valvular heart disease, most often occurs because of

gradual progression of valvular calcification in both normal and congenitally abnormal valves. Assessment of aortic stenosis is most commonly performed with echocardiography, although techniques for quantitative assessment of aortic stenosis with CMR have been developed and increasingly used over the past decade. Echocardiographic assessment generally begins with visual inspection of the valve, usually in the parasternal long-axis and short-axis views. This allows for assessment of valvular morphology, whether it is tricuspid, bicuspid, or some variant; degree of leaflet calcification; and leaflet excursion.

The normal aortic valve consists of three leaflets or cusps: the right coronary, the left coronary, and the noncoronary cusps. Abnormalities of cusp development are some of the most common congenital heart anomalies, the most common of which is bicuspid aortic valve, with two opening leaflets rather than three (Fig. 12-19). The aortic valve can be visualized on echocardiography, although sometimes it can be difficult to distinguish true bicuspid aortic valve from variants, including the presence of a vestigial commissure (raphe). Bicuspid aortic valve, one of the most common congenital anomalies, predisposes to both aortic stenosis and aortic insufficiency.

As discussed above, the degree of aortic stenosis is assessed by estimating both the pressure gradient across the valve and the valve area. Patients with moderate aortic stenosis or higher generally have peak instantaneous velocities of 3.0 m/s and higher, and often higher than 4.0 m/s, corresponding to pressure gradients of 36 and 64 mmHg, respectively. Because pressure gradients across the aortic valve can be underestimated in patients with severe left ventricular dysfunction, estimation of valve area by the continuity principle is the most accurate technique for assessing the severity of the stenosis. However, evaluation of the patient with so-called low-flow or low-gradient aortic stenosis can be challenging and can sometimes require provocative testing such as dobutamine echocardiography. In these cases, it is important to distinguish whether the valve is indeed capable of

opening further or simply behaving like a stenotic valve because of the low-pressure gradient.

Aortic valve areas less than 1.0 cm² are generally considered severe, and valve areas less than 0.6 cm² are considered critical. Because patients with good left ventricular function can often tolerate severe aortic stenosis for a considerable period of time, valve areas or gradients alone should not be used to determine whether an individual patient should undergo aortic valve surgery, as this remains a clinical decision.

Some patients with apparent aortic stenosis actually have subvalvular or even supra-ventricular obstruction. Hypertrophic cardiomyopathy represents the classic form of subvalvular aortic stenosis, but this is usually easily distinguished from aortic stenosis on echocardiography as the valve leaflets can be seen opening during systole. Subaortic membranes can behave very similarly to leaflet aortic stenosis, and the membranes themselves can be very thin and difficult to visualize, although the presence of a murmur, a gradient across the valve with aortic leaflets that appear to open normally, is highly suggestive of a membrane. Supra-ventricular aortic stenosis, although exceedingly rare, also occurs.

The emergence of transcatheter aortic valve intervention as a therapeutic option for patients with severe aortic stenosis who are not optimal candidates for surgical replacement has resulted in a very important clinical role for multimodality imaging. Imaging plays a critical role in preprocedural planning, intraprocedural implantation optimization, and follow-up of these patients. CT plays an important role in defining the eligibility of the proposed access site (CTA of the aorta and iliac arteries) and in defining the anatomic relationships between the aortic valve and aortic root, left ventricle, and coronary ostia. Cardiac CT and transesophageal echocardiography are also used to define the device size. Transesophageal echocardiography is used during the device implantation to ensure the best prosthesis–patient match, to assess prosthesis position and function after deployment, and to identify immediate complications (e.g., aortic insufficiency, paravalvular

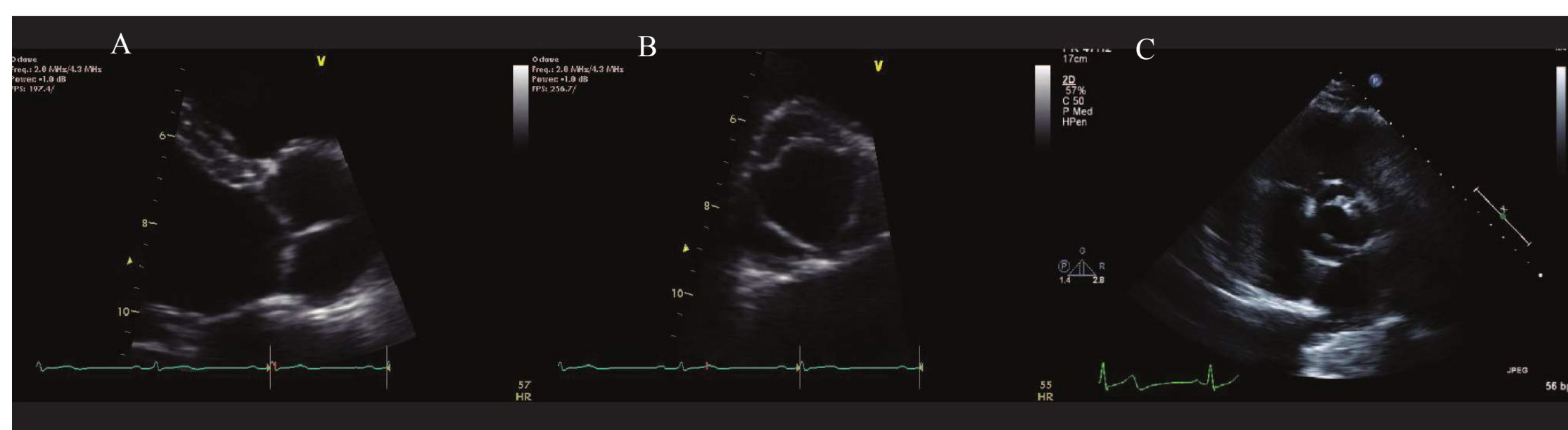


FIGURE 12-19

Normal aortic valve in the parasternal long-axis view (A) and short-axis view (B), and bicuspid aortic valve showing typical 10 o'clock to 4 o'clock leaflet orientation (C).

leak resulting from patient–prosthesis mismatch). Echocardiography is the imaging modality of choice for long-term surveillance.

Assessment of aortic regurgitation

Assessment of aortic regurgitation requires qualitative assessment of the aortic valve structure. Aortic regurgitation is common with congenital abnormalities of the aortic valve, the most common of which is bicuspid aortic valve. Aortic regurgitation often coexists with aortic stenosis, and it is not uncommon for patients to have both severe aortic stenosis and regurgitation. Congenital abnormalities of the aortic leaflets, such as bicuspid aortic valve, are common causes of aortic insufficiency. Dilatation of the aortic root, as occurs in patients with hypertension and other disorders in which aortic dilatation can occur, can also lead to aortic regurgitation even when the valve leaflets are intrinsically normal due to malcoaptation of the leaflets. Aortic root dilatation is common in patients with aortic regurgitation, both as a cause or coexisting lesion, and the aortic root and ascending aorta should be measured and followed in these patients (**Fig. 12-20**).

Because aortic regurgitation can result in dilatation of the left ventricle over time with ultimate reduction in ventricular function, caring for the patient with aortic regurgitation requires serial assessment of ventricular size and function. Patients whose ventricles dilate beyond an end-systolic diameter of 5.5 cm or whose LVEF declines below normal are at significantly higher risk of death or heart failure, and these measures are often used to decide the need for valve surgery. Quantitation of regurgitation itself can be performed using a number of methods. Semiquantitative visual assessment of aortic regurgitant jet width and depth by color flow Doppler remains the most used. The jet diameter as a ratio of the left ventricular outflow tract diameter proximal to the valve represents one of the most reliable indices of severity and correlates well with angiographic assessment. Similarly, the vena contracta, which represents the smallest diameter of the regurgitant flow at the level of the valve, can be used to assess the severity of aortic regurgitation. Other Doppler-based methods include assessing the pressure half-time, or rate of

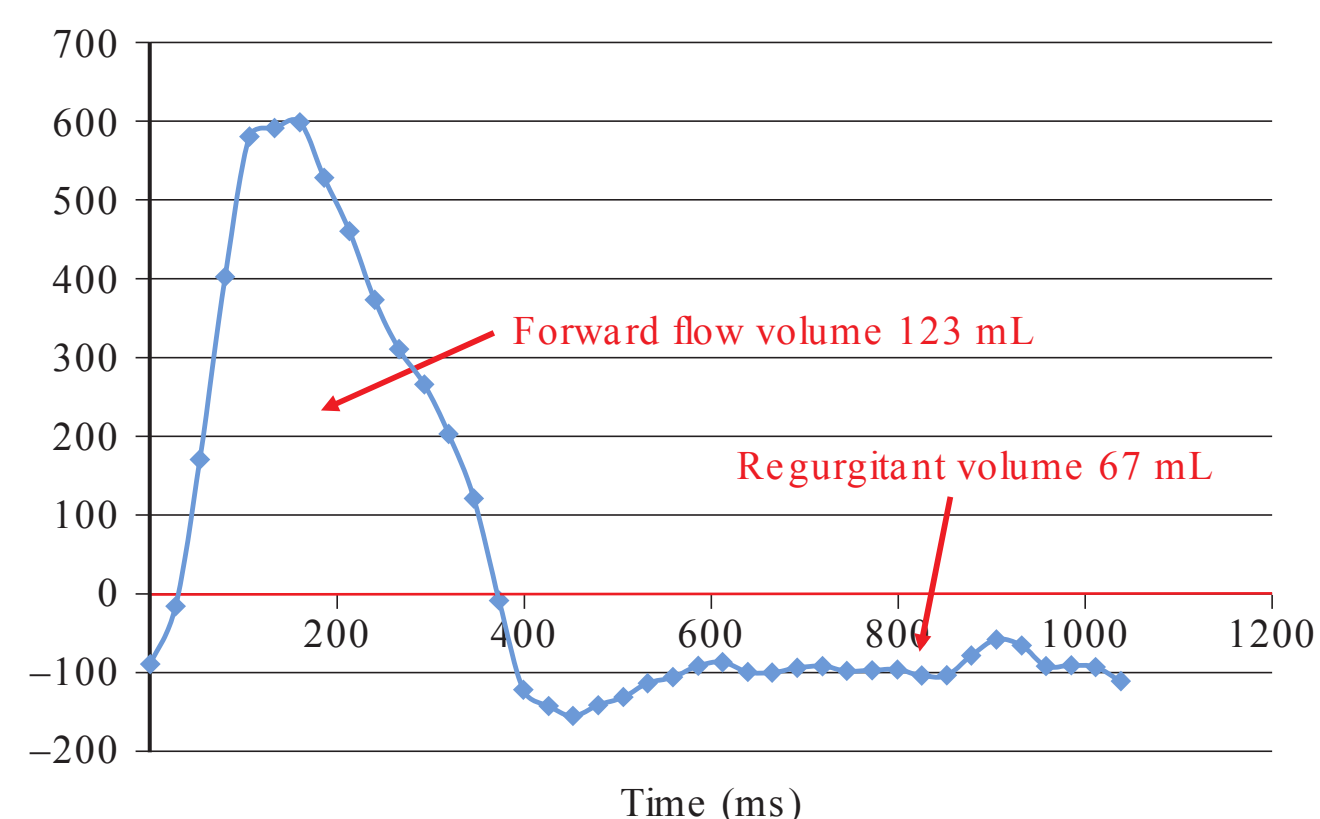


FIGURE 12-21

The resultant flow curve generated from phase contrast imaging demonstrates a forward flow of 123 mL and a regurgitant volume of 67 mL, yielding a regurgitant fraction of 54% indicating severe aortic regurgitation.

decline of the pressure gradient between the aorta and left ventricle, a measure of acuity of aortic regurgitation, and assessing aortic flow reversal in the descending aorta. The regurgitant volume can be calculated by comparing the flow across the aortic and pulmonic valves, assuming the pulmonic valve is competent.

CMR offers a number of advantages over echocardiography in the assessment of aortic regurgitation. CMR can be more accurate than echocardiography for assessing small changes in cardiac size or function that can occur over time in patients with aortic insufficiency. In addition, CMR techniques can very accurately quantify regurgitant volume in patients with aortic insufficiency, a known limitation of echocardiography. CMR can also capture three-dimensional imaging of the aortic size that in some cases can be helpful in determining the etiology of the aortic regurgitation or in monitoring the patient (**Fig. 12-21** and **Video 12-6**).

Assessment of mitral regurgitation

The normal mitral valve consists of an anterior and posterior leaflet in a saddle shape configuration (**Fig. 12-22**). The leaflets are attached to the papillary muscles via chordae tendineae that insert on the ventricular side of

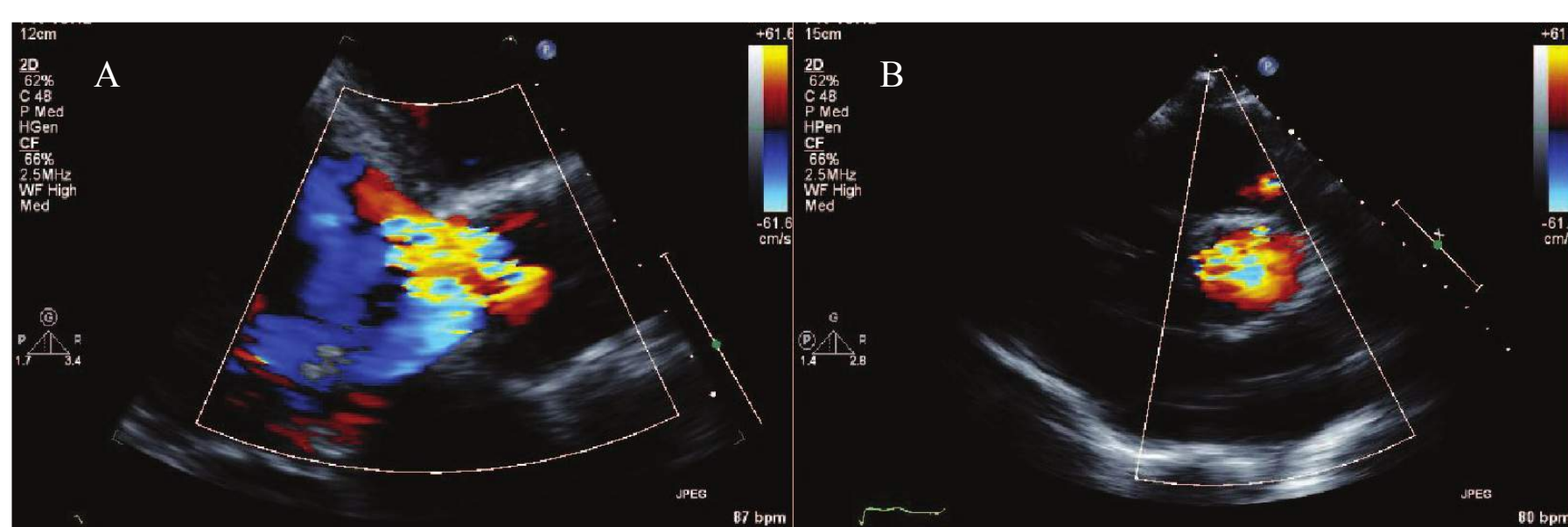


FIGURE 12-20

Aortic regurgitation visualized by color flow Doppler in the parasternal long-axis view (A) and the parasternal short-axis view (B).

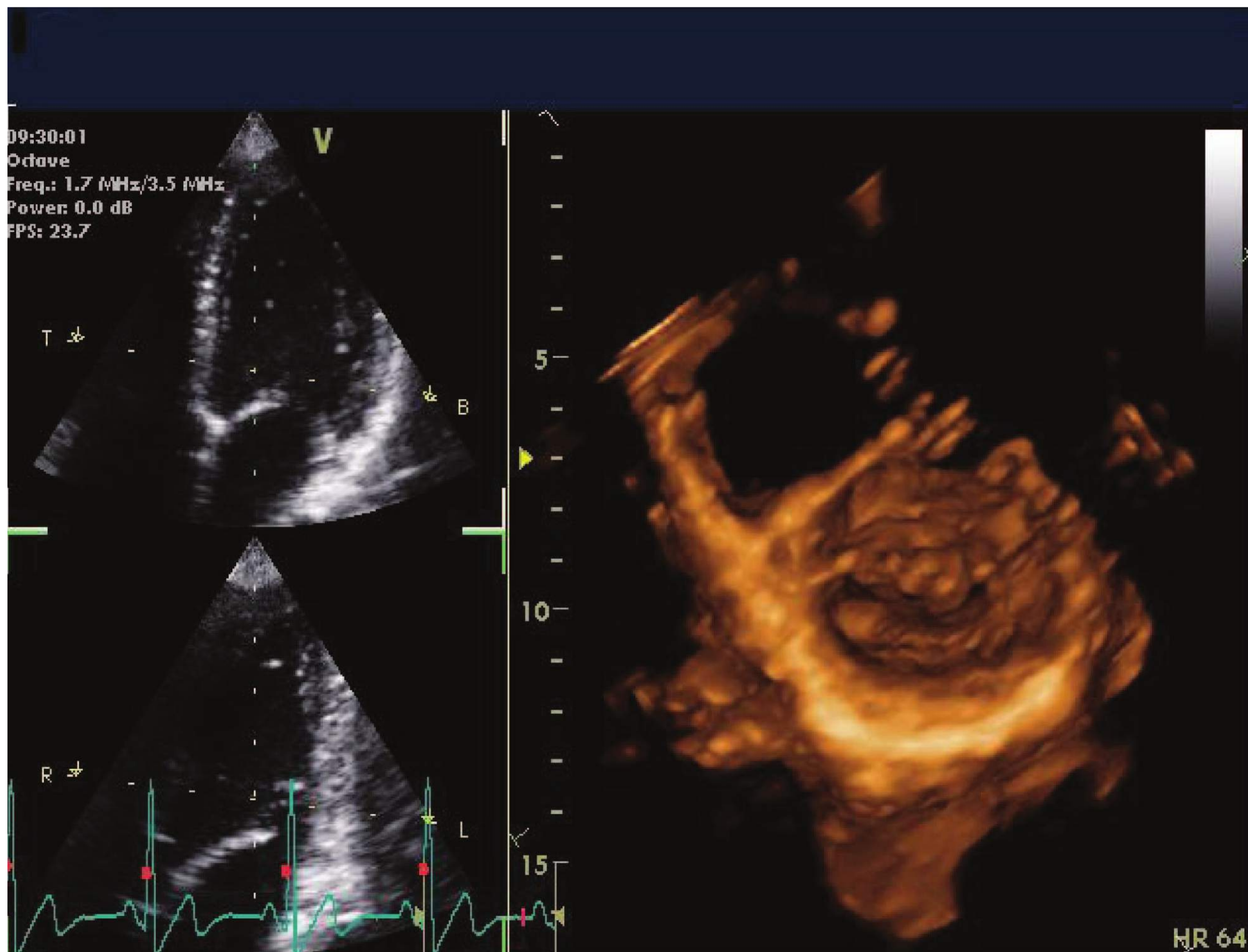


FIGURE 12-22

Normal mitral valve in two-dimensional views (left) and with three-dimensional imaging (right).

the leaflets. Mitral regurgitation can occur due to abnormalities of the leaflets, the chordal structures, or the ventricle, or any combination of these (Fig. 12-23).

Mitral valve prolapse, in which one leaflet moves behind the plane of the other leaflet, can be due to myxomatous degeneration of the valves and leaflet redundancy, disruption of chordal structures secondary to

degenerative disease, or papillary muscle rupture or dysfunction following myocardial infarction. Regurgitant jets can be visualized using color flow Doppler. The velocity of regurgitant jets is driven by the pressure gradient between the two chambers. The velocity tends to be quite high for left-sided regurgitant lesions, including mitral regurgitation and aortic regurgitation, resulting in

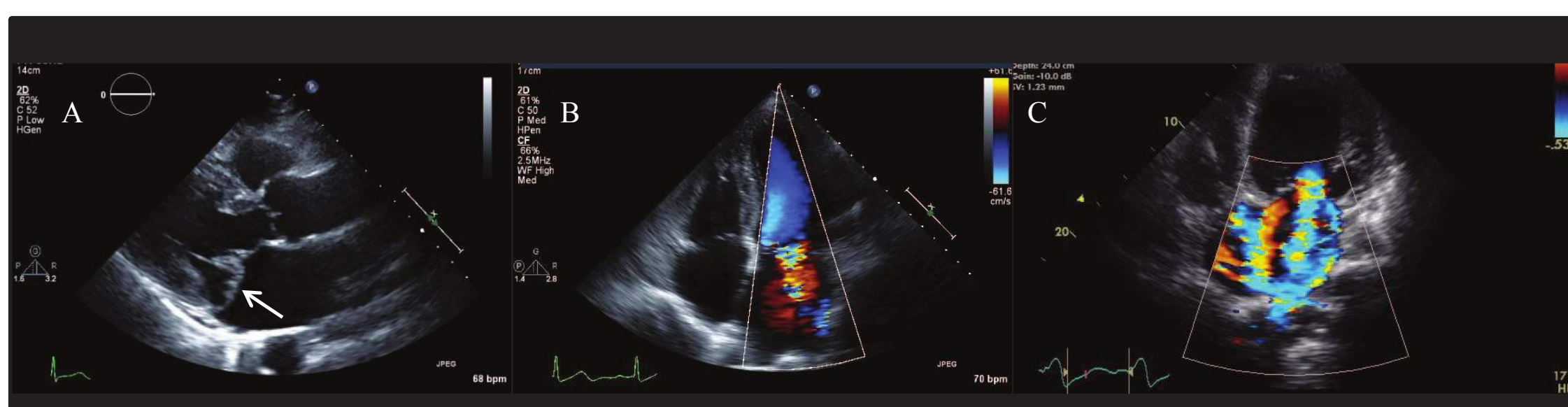


FIGURE 12-23

A. Mitral valve prolapse with posterior leaflet visualized prolapsing behind the plane of the anterior leaflet (arrow). B. Color flow Doppler showing mitral regurgitation in a patient with mitral

valve prolapse. C. Severe functional mitral regurgitation in a patient with a dilated left ventricle.

turbulent jets on color flow Doppler (Fig. 12-23). Visual estimation of color flow Doppler is generally sufficient for qualitative assessment of regurgitant severity but can dramatically under- or overestimate regurgitation severity, particularly when regurgitant jets are quite eccentric. For this reason, quantitative assessment is generally recommended, especially when making clinical decisions about surgical intervention. The PISA method is generally used for quantitative assessment of severity of mitral regurgitation. This method relies on estimation of the velocity of flow acceleration at a specific distance proximal to the valve with the assumption that the flow accelerates in concentric hemispheres.

As with aortic insufficiency, assessment of ventricular structure and function is also integral in the evaluation of mitral regurgitation. Although some patients have mitral regurgitation due to intrinsic abnormalities of the valve itself, in others, the valve can be relatively normal but the mitral regurgitation can be secondary to dilatation and remodeling of the left ventricle. So-called functional mitral regurgitation is generally secondary to apical displacement of the papillary muscles in a dilated ventricle, resulting in the leaflets of the mitral valve being pulled toward the apex of the heart, resulting in poor coaptation during systole and resultant relatively central mitral regurgitation. This type of mitral regurgitation can generally be distinguished from intrinsic mitral valve disease, and the surgical or procedural treatment of these conditions can be different. Knowledge of the etiology of mitral regurgitation can be important for a surgeon planning mitral valve surgery. Moreover, new procedural approaches to mitral valve disease may be different depending on the etiology.

Ventricular dilatation is an important predictor of outcome in patients with mitral regurgitation of any cause. It is important to realize that in a patient with significant mitral regurgitation, a large portion of the blood being ejected from the left ventricle with every beat is regurgitant, thus artificially increasing the ejection fraction. Thus, an ejection fraction of 55% in a patient with severe

mitral regurgitation may actually represent substantial reduction in myocardial systolic function.

CMR can be helpful in evaluating mitral regurgitation in a subset of patients when echocardiographic assessment is inadequate. CMR can directly quantify regurgitant volume of the mitral regurgitant jet or indirectly quantify regurgitant volume by measuring the difference of left ventricular stroke volume and aortic forward flow.

Assessment of mitral stenosis

Rheumatic mitral disease remains the most common cause of mitral stenosis, although mitral stenosis can also result from severe calcification of the mitral leaflets. Rheumatic mitral stenosis has a distinct appearance characterized by tethering at the leaflet tips and relative pliability of the leaflets themselves, resulting in a hockey stick–type deformation particularly of the anterior leaflet (Fig. 12-24). Narrowing of the mitral orifice impedes flow from the left atrium to the left ventricle, resulting in increased pressures in the left atrium, which are then transmitted backward into the pulmonary vasculature and the right side of the heart. When mitral stenosis is suspected, echocardiography can be useful for determining etiology (specifically whether it is rheumatic or not), estimating the valve areas and gradients across the valve, assessing the left atrium, and assessing right ventricular size and function. Assessment of left atrial size and right ventricular size and function is particularly useful in helping determine the severity of the mitral stenosis.

MYOCARDIAL INFARCTION AND HEART FAILURE

Role of imaging after myocardial infarction

Imaging can be particularly useful in the immediate and long-term follow-up of patients with myocardial infarction. As discussed earlier in the chapter, CMR is

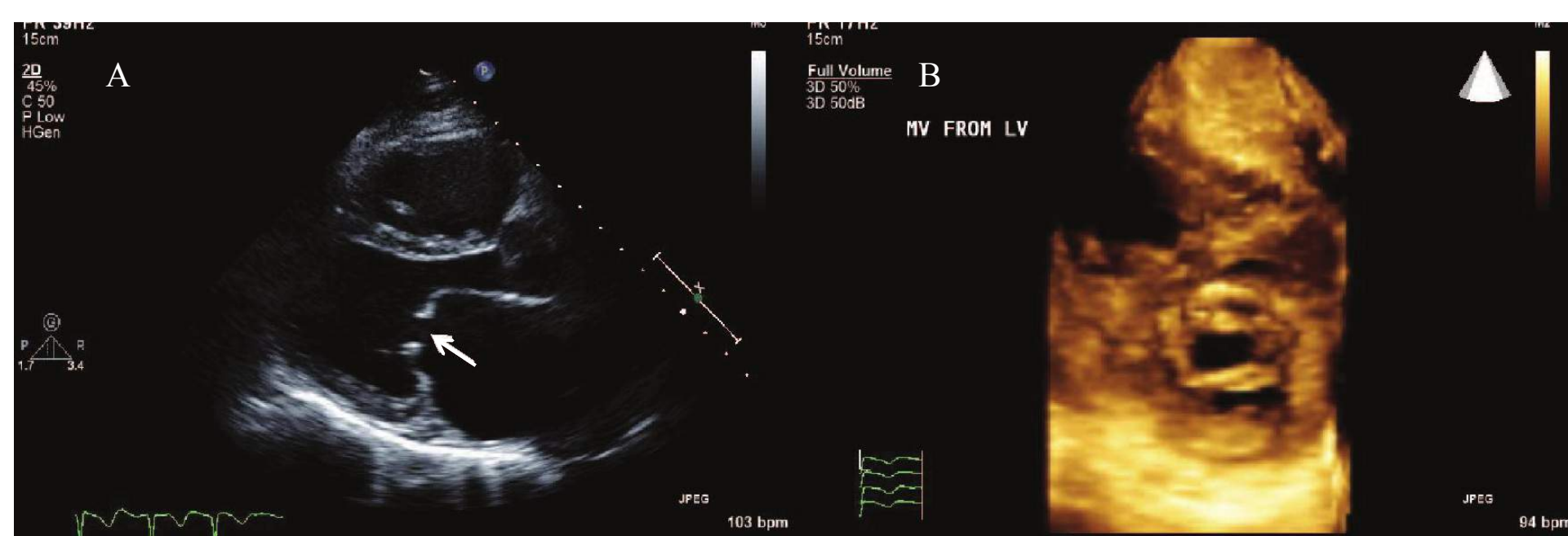


FIGURE 12-24

A. Rheumatic mitral stenosis showing pliable leaflets tethered at the tips (arrow). Note the characteristically enlarged left atrium. B. Mitral stenosis visualized from a three-dimensional echocardiogram.

the best technique for direct assessment of infarcted myocardium. LGE imaging by CMR provides accurate delineation of infarct size and morphology. In a recent multicenter study, LGE imaging by CMR identified infarct location accurately and detected acute and chronic infarcts with a sensitivity of 99% and 94%, respectively. With an in-plane spatial resolution of 1.5–2 mm and a high contrast-to-noise ratio, LGE by CMR has excellent sensitivity in detecting small areas of myocardial scar. In addition, regions of microvascular obstruction (no-reflow) can be seen as dense hypoenhanced areas within the core of a bright region of infarction. Both the presence of LGE and microvascular obstruction are markers of increased clinical risk.

While echocardiography is often used to assess myocardial function immediately after myocardial infarction, myocardial stunning is common in the early post-myocardial infarction period, especially in patients who undergo reperfusion therapy. In these patients, either partial or complete recovery of ventricular function is common within several days, so that early estimation of ejection fraction may be misleading. In patients with uncomplicated myocardial infarction, imaging can generally be deferred for several days so that a more accurate assessment of cardiac function, including regional wall motion, can be assessed (Fig. 12-25).

Echocardiography is the best method for assessment of patients with suspected mechanical complications after myocardial infarction. These include mitral regurgitation secondary to either papillary muscle dysfunction or rupture of papillary muscle head, ventricular septal defect, or even cardiac rupture. A new severe systolic murmur should raise suspicions for either severe mitral regurgitation or ventricular septal defect. While cardiac rupture is often catastrophic, contained ruptures, also known as pseudoaneurysms, can occur, and early diagnosis and surgical treatment are the best way

to maximize survival. The presence of thrombus within the pericardial space following myocardial infarction should immediately raise suspicion of myocardial rupture and represents a surgical emergency.

Some patients demonstrate progressive left ventricular dilatation and dysfunction, known as cardiac remodeling, after myocardial infarction. Assessment of cardiac function and regional wall motion is useful in the follow-up period, generally between 1 and 6 months following infarction. The persistence of left ventricular systolic dysfunction following infarction is used to determine the type of therapy (e.g., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are typically used in patients with systolic dysfunction following myocardial infarction).

In patients with acute or subacute myocardial infarction, investigation of residual ischemia and/or viability is occasionally an important clinical question, especially among those with recurrent symptoms after myocardial infarction (Fig. 12-26). All cardiac imaging techniques can provide information regarding myocardial viability and ischemia. In the absence of definitive trials offering head-to-head comparisons between techniques in large series of patients, uncertainty persists concerning the relative accuracies of each method for predicting functional and prognostic benefit after revascularization. Thus, one should exercise caution in the interpretation of the relative diagnostic accuracy of each imaging technology. Nevertheless, the available data suggest that radionuclide imaging, especially PET, is highly sensitive, with higher negative predictive value than dobutamine echocardiography. In contrast, dobutamine echocardiography tends to be associated with higher specificity and positive predictive accuracy than the radionuclide imaging methods. The experience with CMR suggests that it offers similar predictive accuracies as those seen with dobutamine echocardiography.

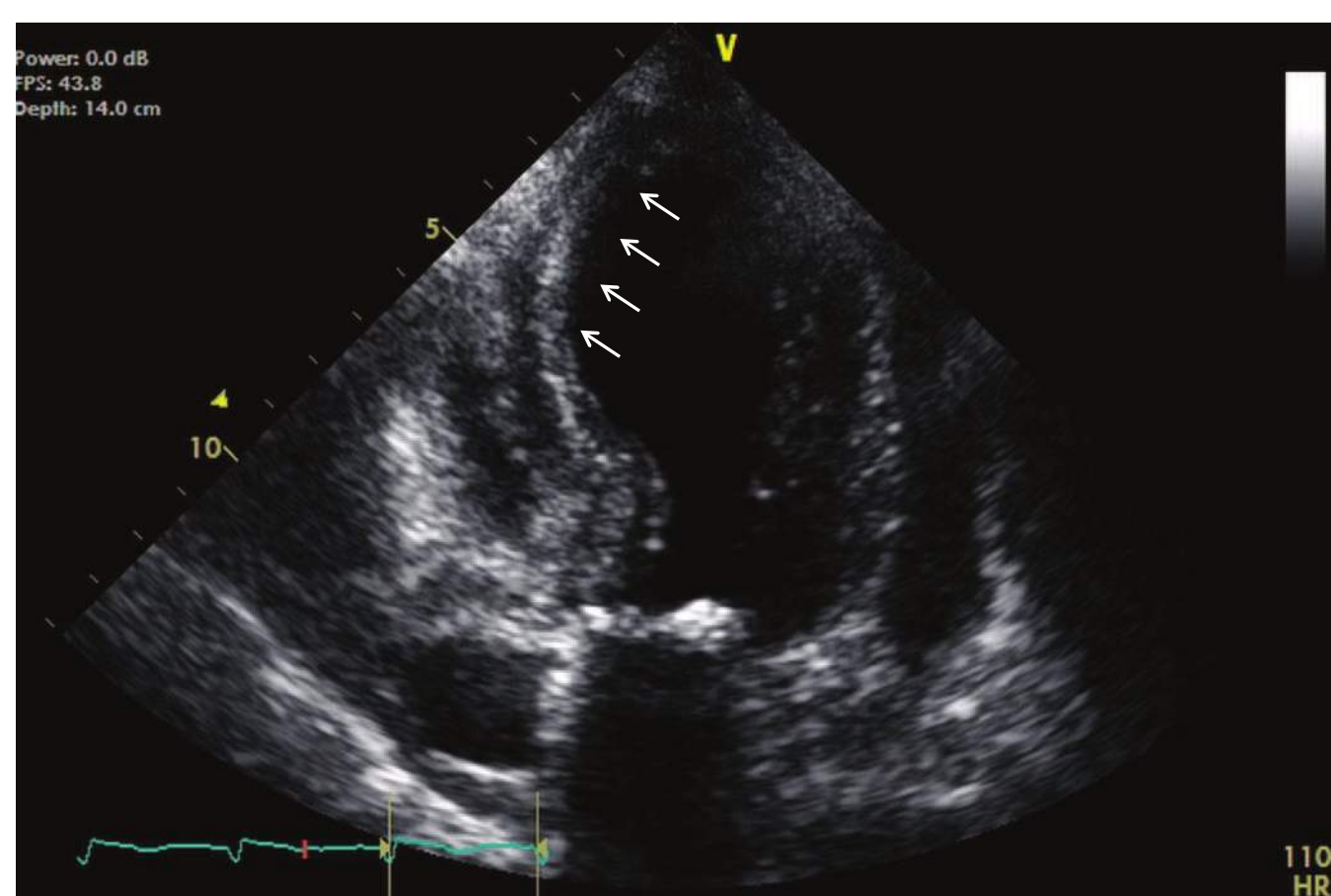


FIGURE 12-25

Acute left anterior descending artery distribution myocardial infarction at end systole showing akinetic region (arrows).

Role of imaging in new-onset heart failure

Echocardiography is usually a first-line test in patients presenting with new-onset heart failure. As discussed above, this test provides a direct assessment of ventricular function and can help distinguish patients with reduced ejection fraction from those with preserved ejection fraction. In addition, it provides additional structural information including an assessment of valves, myocardium, and pericardium.

Although coronary angiography is commonly performed in patients with reduced ejection fraction, the determination of heart failure etiology in an individual patient may be difficult even if angiographically obstructive CAD is present. Indeed, patients with heart failure and no angiographic CAD may have typical angina or regional wall motion abnormalities on noninvasive imaging, whereas patients with angiographically

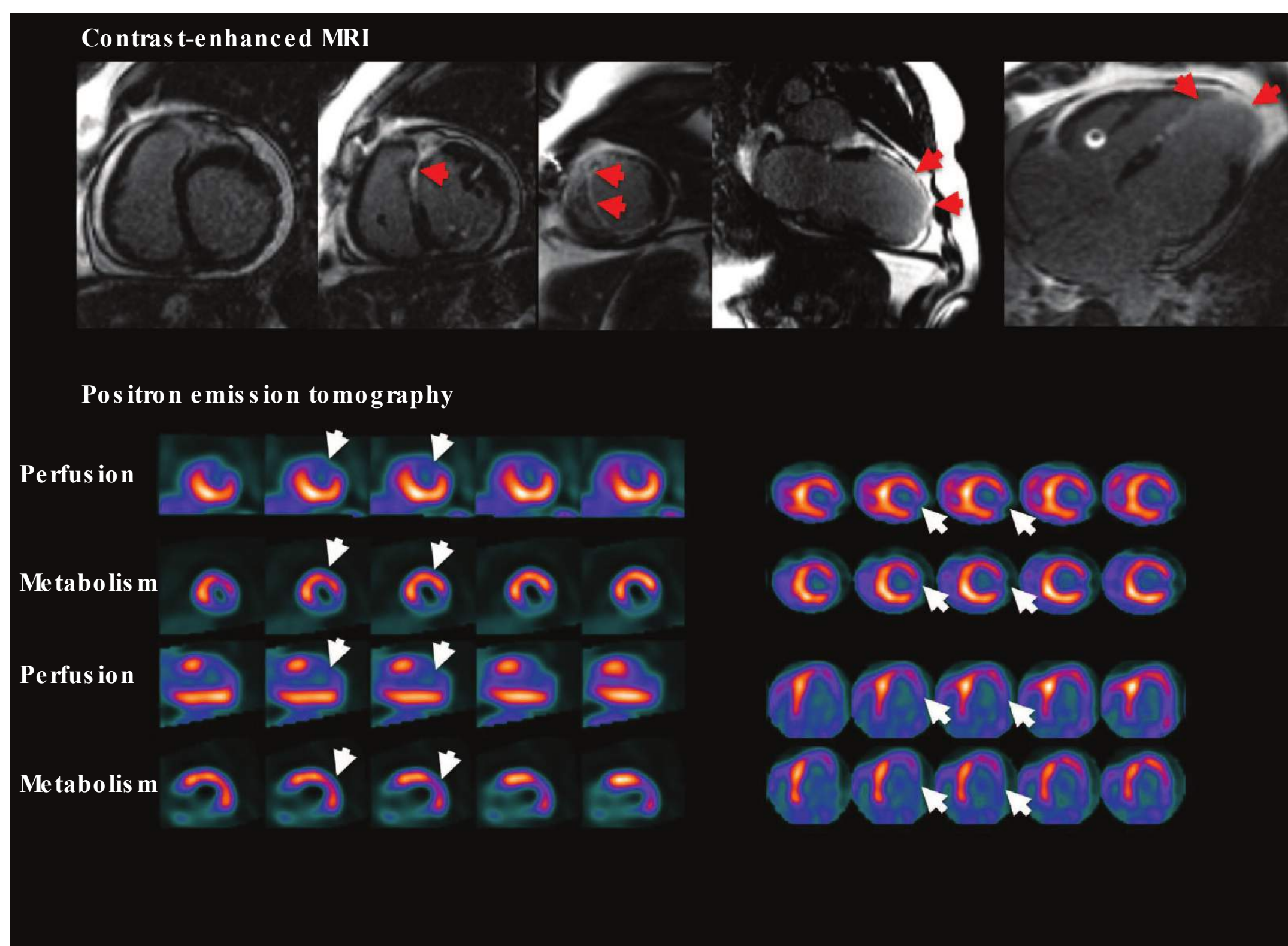


FIGURE 12-26

Examples of myocardial viability patterns obtained with cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET) in three different patients with coronary artery disease. The top panel demonstrates extensive late gadolinium enhancement (bright white areas) involving the anterior, anteroseptal, and apical left ventricular walls (arrows), consistent with myocardial scar and nonviable myocardium. The lower left panel demonstrates rubidium-82

myocardial perfusion and ^{18}F -fluorodeoxyglucose (FDG) images showing a large and severe perfusion defect in the anterior, anterolateral, and apical walls, indicating preserved glucose metabolism (so-called perfusion-metabolic mismatch) consistent with viable myocardium. The right lower panel shows similar PET images demonstrating concordant reduction in perfusion and metabolism (so called perfusion-metabolic match) in the lateral wall, consistent with nonviable myocardium.

obstructive CAD may have no symptoms of angina or history of myocardial infarction. Thus, the appropriate classification for any given patient is not always clear, and it often requires the complementary information of coronary angiography and noninvasive imaging. Stress radionuclide imaging and echocardiography can be helpful in delineating the extent and severity of inducible myocardial ischemia and viability. Multiparametric CMR can be quite helpful in the differential diagnosis of heart failure etiologies. Apart from quantifying left and right ventricular volumes and function, CMR can provide information about myocardial ischemia and scar. The pattern of LGE helps differentiate infarction (typically starting in the subendocardium and involving a coronary territory) from other forms of infiltrative or inflammatory cardiomyopathies (typically involving the mid- or subepicardial layers without following a coronary distribution) (Fig. 12-27). In addition, it can assess the presence of myocardial edema (e.g., myocarditis)

and quantify myocardial iron deposition that can potentially lead to cardiac toxicity. Infiltrative cardiomyopathy such as amyloidosis typically has a restrictive cardiomyopathy pattern (bilateral atrial enlargement and biventricular increased wall thickness). CMR of patients with cardiac amyloidosis often also demonstrates a characteristic pattern of diffuse endocardial infiltration of the left ventricle and the atria (Fig. 12-27). Hypertrophic cardiomyopathy has variable degree of increased ventricular thickness, and often is seen to have outflow obstruction and intense LGE in regions with marked hypertrophy (Fig. 12-28). CMR also can quantify myocardial iron content in patients at risk of iron-overload cardiomyopathy (Video 12-7).

PET metabolic imaging has a complementary role in the evaluation of inflammatory cardiomyopathies, especially sarcoidosis. In patients with suspected cardiac sarcoidosis, the presence of focal and/or diffuse glucose uptake can help identify areas of active sarcoidosis. In

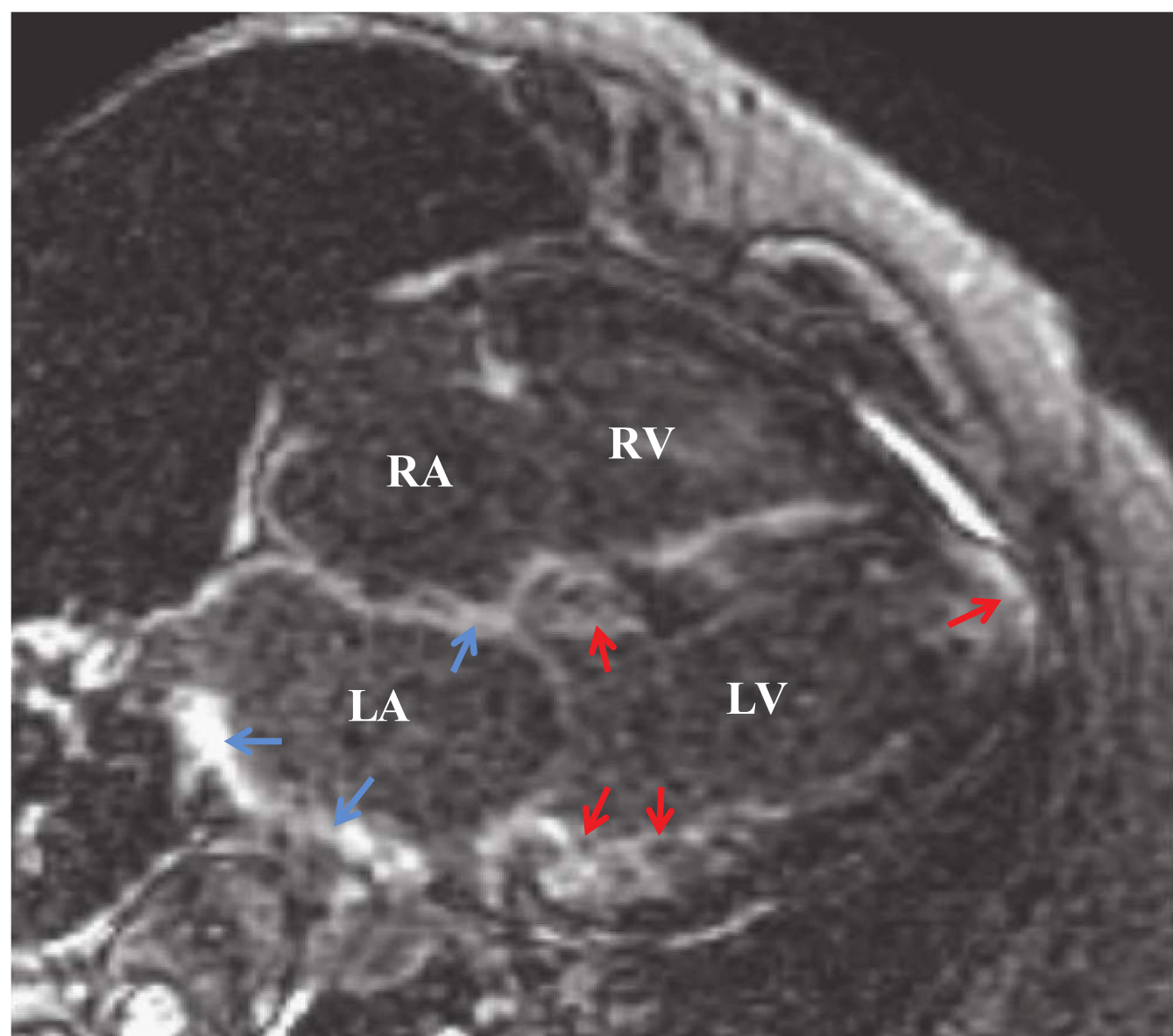


FIGURE 12-27

A case of cardiac amyloidosis. Note on this late gadolinium enhancement image that there were multiple foci of gadolinium accumulation in the left ventricle (LV) myocardium (red arrows), as well as the left atrial (LA) walls (blue arrows). The LV walls were markedly increased in thickness, and both atria were dilated, consistent with a restrictive cardiac morphology. The blood pool signal was diminished after contrast injection, which was consistent with high burden of amyloid disease in other organs that causes gadolinium concentration in the blood to rapidly go down. RA, right atrium; RV, right ventricle.

addition, for patients undergoing immunosuppressive therapy, PET is frequently used to monitor therapeutic response (**Fig. 12-29**). In patients with ischemic cardiomyopathy, radionuclide imaging in general and PET in particular are frequently used to quantify the presence and extent of myocardial ischemia and viability to assist with clinical decision making related to myocardial revascularization (**Fig. 12-26**).

ASSESSING CARDIAC FUNCTION IN PATIENTS UNDERGOING CANCER TREATMENT

Therapies used to treat cancer can adversely affect the cardiovascular system. As the efficacy of cancer treatment and survival improve, many patients are presenting with late adverse consequences from chemotherapy and/or radiation therapy on cardiovascular function. Thus, the morbidity and mortality from late cardiovascular complications threaten to offset the early gains in cancer survival, especially among children and young adults. Early recognition and treatment of cardiomyocyte injury are critical for successful application of preventative therapies, but difficult because the adverse effects on cardiac function are a relatively late manifestation after exposure to anticancer therapy.

The accepted standard for clinical diagnosis of cardiotoxicity is defined as a $>5\%$ reduction in LVEF to $<55\%$ with symptoms of heart failure, or a $>10\%$ drop

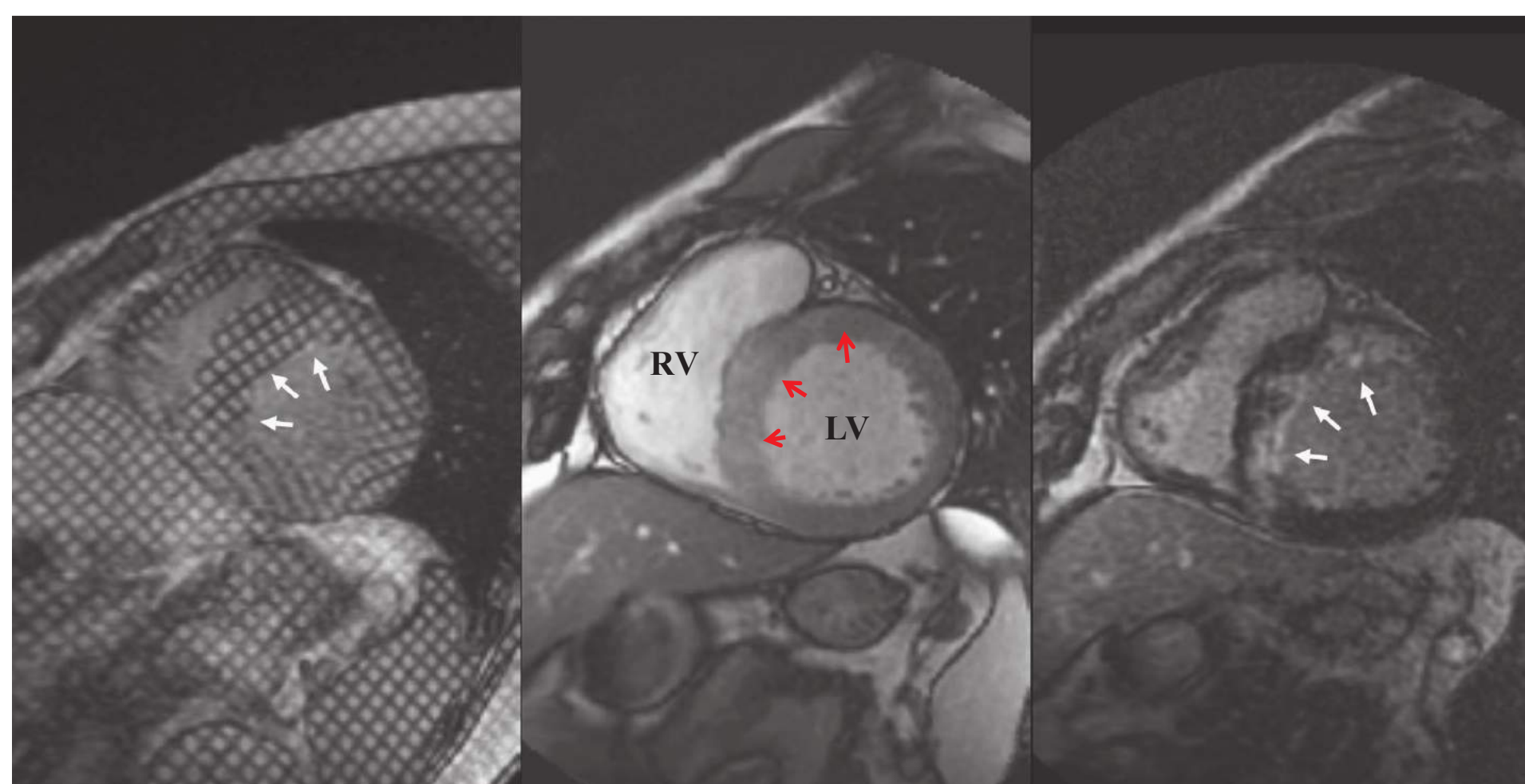


FIGURE 12-28

This figure demonstrates three pulse sequence techniques by cardiac magnetic resonance that are often used to assess patients with hypertrophic cardiomyopathy, all displayed in the mid short-axis scan plane. The center panel demonstrates that the left ventricle (LV) was markedly thickened in its wall thickness especially in the LV septum (red arrows). This finding was matched by marked regions of late gadolinium enhancement (LGE), which was consistent with fibrosis in these segments (right panel, white arrows).

The left panel was cine myocardial tagging in the same slice plane. Myocardial tagging is used to assess the normal intramyocardial strain by assessing distortion of the myocardial grids during systole. In this case, despite normal-appearing systolic radial wall thickening, the myocardial strain as assessed by the distortion of grids was markedly reduced (left panel, white arrows). This finding is consistent with substantial myofibril disarray in the anterior and anteroseptal segments in this patient. RV, right ventricle.

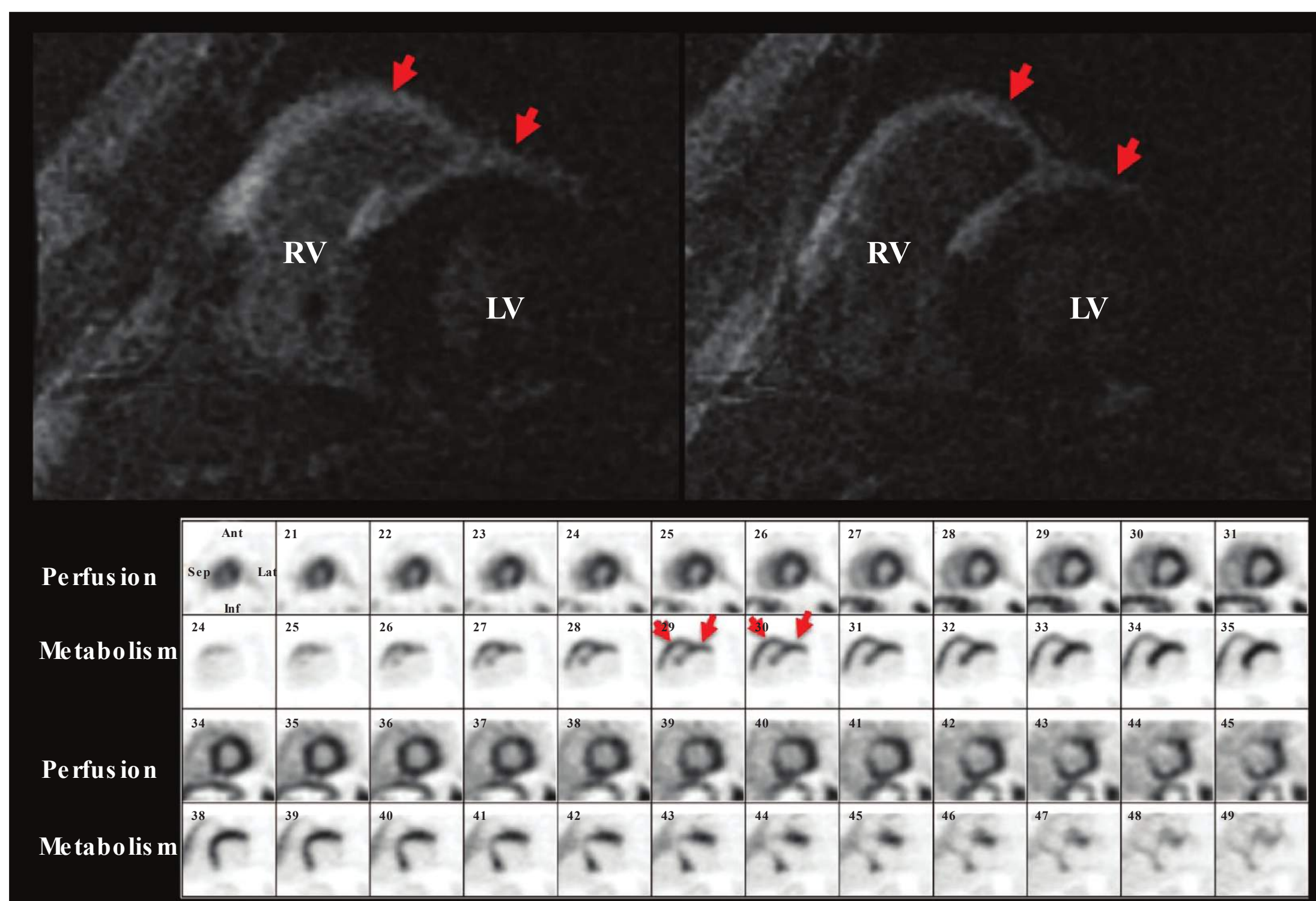


FIGURE 12-29

Representative cardiac magnetic resonance (CMR; top panel) and positron emission tomography (PET; lower panel) images from a 45-year-old male presenting with complete heart block. The CMR images demonstrate extensive late gadolinium enhancement in the subepicardial left ventricular

(LV) anterior and anteroseptal walls and also in the right ventricular (RV) free wall (arrows). The PET images demonstrate extensive fluorodeoxyglucose uptake in the same areas, most consistent with active inflammation due to sarcoidosis.

in LVEF to $<55\%$ in patients who are asymptomatic. Thus, noninvasive imaging plays a major role in diagnosing and monitoring for cardiac toxicity in patients undergoing cancer treatment. Radionuclide angiography has been the technique of choice for quite some time. However, this is rapidly changing, and echocardiography now plays a major role in this application.

Recently, more novel imaging approaches have been advocated, including deformation imaging with echocardiography and fibrosis imaging with CMR. These techniques have shown promising results in experimental animal models and in humans. In addition, there are also proof-of-concept studies in animal models using molecular imaging approaches targeting the mechanisms of cardiac toxicity (e.g., apoptosis and oxidant stress), which can presumably provide the earliest signs of the off-target effects of these therapies. However, all of these techniques are currently considered experimental.

PERICARDIAL DISEASE

The fibroelastic pericardial sac surrounding the heart consists of a visceral, or epicardial, layer and a parietal layer, with a generally small amount of pericardial fluid

in between layers. The pericardium is generally quite pliable and moves easily with the heart during contraction and relaxation. Abnormalities of the pericardium can affect cardiac function primarily by impairing the heart's ability to fill. Inflammation of the pericardium can lead to an accumulation of fluid between the two layers, or pericardial effusion, which can be visualized by echocardiography, CMR, or CT. Other reasons for accumulation of pericardial fluid include infection, malignancy, and bleeding into the pericardium. The latter can be the result of catastrophic processes such as trauma, cardiac rupture, perforation in the setting of a cardiac procedure, cardiac surgery, or dissection of the aorta with extension in the pericardium.

Echocardiography remains the initial test of choice for assessing pericardial disease, especially effusions (Fig. 12-30). Moreover, echocardiography can be useful in evaluating for pericardial constrictive physiology, in which a thick noncompliant pericardium impairs cardiac filling. The location, size, and physiologic consequences of accumulated pericardial effusion can generally easily be determined by echocardiography. Pericardial tamponade occurs when enough pericardial fluid accumulates so that the intrapericardial

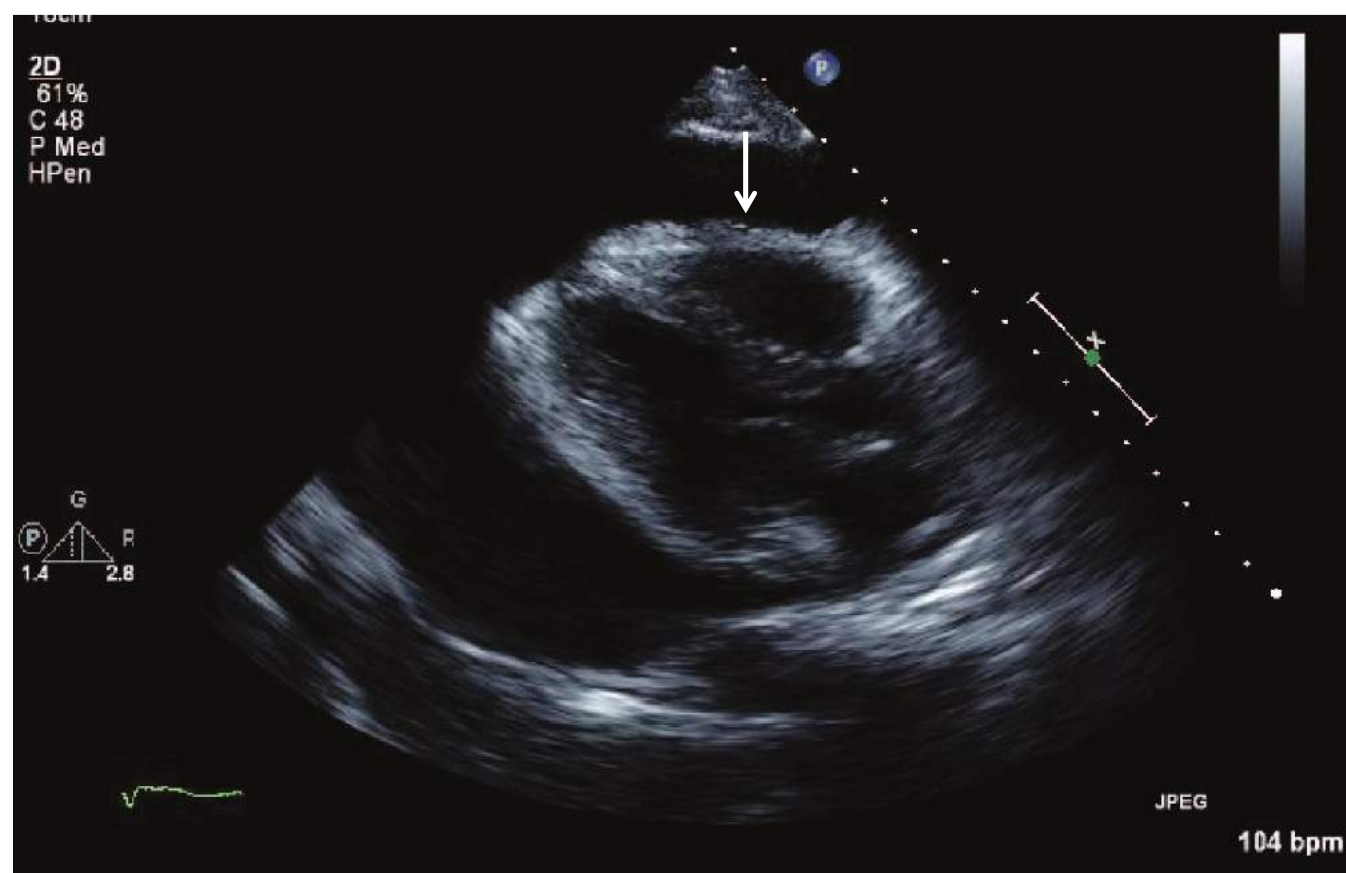


FIGURE 12-30

Pericardial effusion with tamponade physiology. The right ventricle (arrow) is small and collapsing in end diastole due to increased pericardial pressure.

pressure exceeds filling pressures of the heart, generally the right ventricle. The balance between intrapericardial pressure and ventricular pressure is more important than the extent of fluid accumulation. Conditions in which pericardial effusions accumulate over a long period of time, as can be the case in the setting of malignant effusions, can lead to large pericardial fluid accumulations without the classic hemodynamic findings associated with pericardial tamponade. In contrast, rapid accumulations of pericardial fluid, such as those that occur due to cardiac rupture or perforation, can lead to tamponade physiology without very large effusions. In patients with suspected pericardial effusion or tamponade, echocardiography can usually be performed rapidly, at the bedside, and even by operators with limited skill. The distance from the parietal to the visceral pericardial layer can be measured, and when this exceeds approximately 1 cm, an effusion is considered significant. Echocardiographic features suggestive of tamponade include diastolic collapse of the right ventricular free wall, suggestive of pericardial pressures that exceed right ventricular filling pressures, and Doppler evidence of respiratory flow variation, which is the Doppler equivalent of pulsus paradoxus. Despite the benefits of echocardiography in suspected pericardial tamponade, the diagnosis of tamponade remains a clinical diagnosis, and other important features, such as patient's blood pressure in the presence of pulsus paradoxus, needs to be taken into account when considering therapeutic options.

Chronic inflammation of the pericardium can lead to thickening and potentially calcification of the parietal pericardium, resulting in pericardial constriction in which diastolic filling can be severely impaired. In these cases, filling of the ventricles comes to an abrupt halt when the volume of ventricular filling is impaired

by the constricting pericardium. Assessment of pericardial thickness in these patients is important, but it is just as important to note that approximately one in five patients with severe pericardial constriction have no significant pericardial thickening by imaging or at surgery. Thus, a lack of thickened pericardium does not rule out pericardial constriction, and patients' signs and symptomatology and physiologic evidence of constriction should be assessed independently. Pericardial constriction typically demonstrates marked respiratory changes in diastolic flow on Doppler echocardiography, in contrast to restrictive cardiomyopathy, but substantial overlap exists. CT and CMR offer tomographic, whole-heart assessment of pericardial thickening and other anatomy abnormalities in pericardial constriction (enlarged atria, vena cava, pleural and pericardial effusions) (Fig. 12-31 and Video 12-8). CMR offers the additional information of pericardial fibrosis and inflammation by LGE imaging, as well as evidence of constrictive physiology (e.g., regional relaxation concordance due to myocardial adhesions, paradoxical septal motion at rest or during Valsalva maneuver).

CARDIAC THROMBUS AND MASS

Echocardiography is usually the modality that first detects the presence of a cardiac mass. Differential diagnoses of an intracardiac mass most often include thrombus, tumor, or vegetation. Given their unrestricted

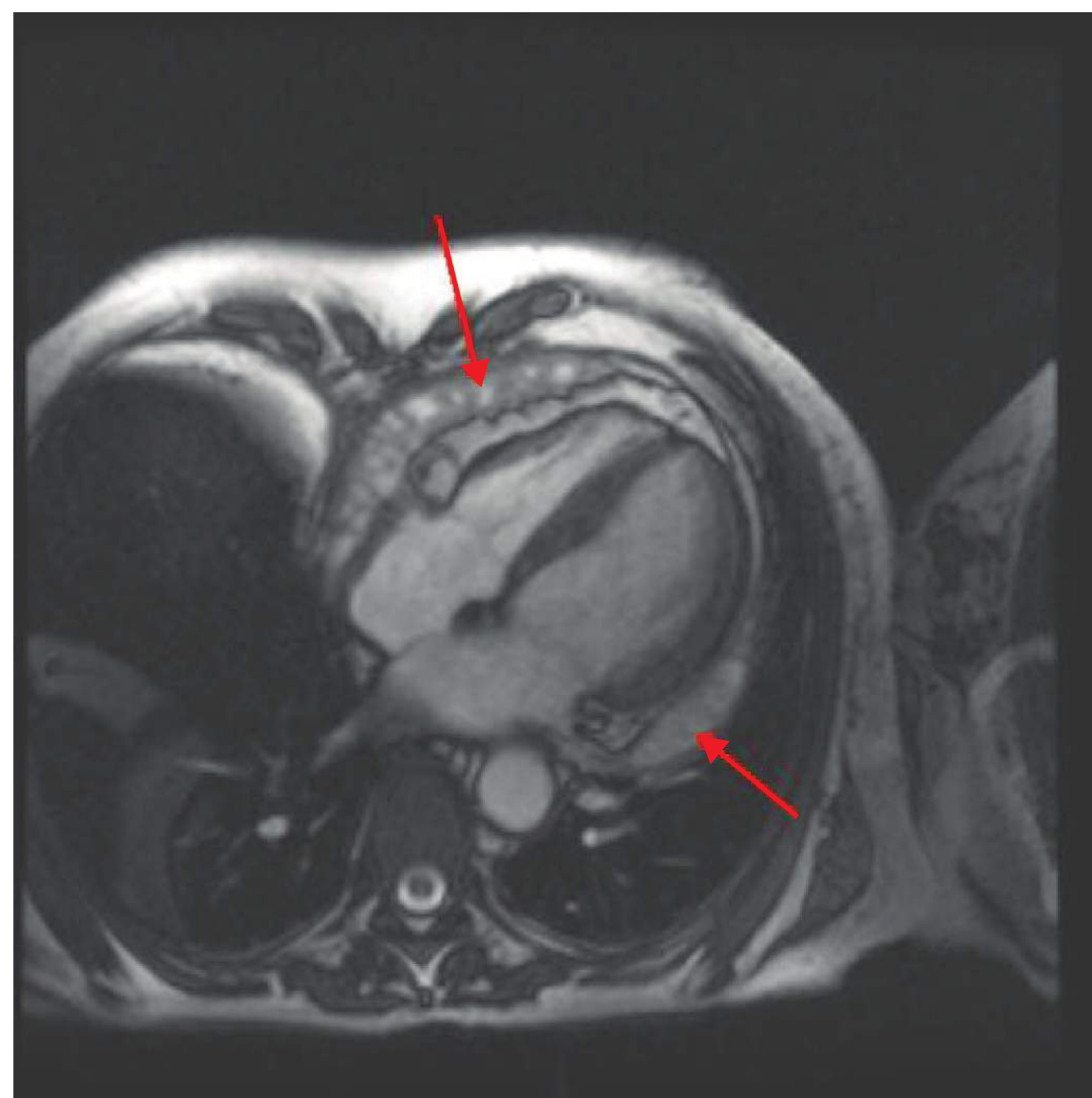


FIGURE 12-31

A female patient developed pericardial constriction and right heart failure, secondary to radiation therapy for breast cancer. Note the multiple pericardial adhesions (red arrows).

tomographic views and multiplanar three-dimensional imaging, CMR and CT can complement echocardiography by further characterizing the physical features of the cardiac mass. Compared to CT, CMR has the advantage of higher tissue contrast differentiation, more robust cine imaging, and the use of multifaceted techniques within the same imaging session to determine the physiologic characteristics of the mass. Gadolinium contrast enhancement patterns of increased capillary perfusion can help to determine the presence and extent of vascularity within the mass, relevant for differentiating tumor from thrombus. Structures that are known to mimic a cardiac mass include (1) anatomic variants, such as the Eustachian valve, Chiari network, crista sagittalis or terminalis, and the right ventricular moderator band, and (2) “pseudotumors,” such as interatrial septal aneurysm, coronary or aortic aneurysm, lipomatous hypertrophy of interatrial septum, hiatal hernia, or a catheter/pacemaker lead. A number of coexisting conditions should raise the likelihood of a cardiac thrombus (**Fig. 12-32**), including regional wall motion abnormality from infarction or ventricular aneurysm, atrial fibrillation leading to slow flow in the left atrial appendage, or presence of venous catheters or recent endovascular injury. CMR has the advantage of being able to assess regional wall motion and infarction or ventricular aneurysm in matching scan planes, adjacent to the cardiac thrombus, using cine and LGE imaging, respectively. For ventricular thrombus, gadolinium-enhanced LGE imaging can detect thrombus at a higher sensitivity than echocardiography by depicting high-contrast difference between the dark thrombus and its adjacent structures and by imaging in three dimensions. In addition, mural thrombus does not enhance on first-pass perfusion and often has a characteristic “etched” appearance (black border surrounding a bright center) on LGE imaging, thus providing higher diagnostic specificity than anatomic

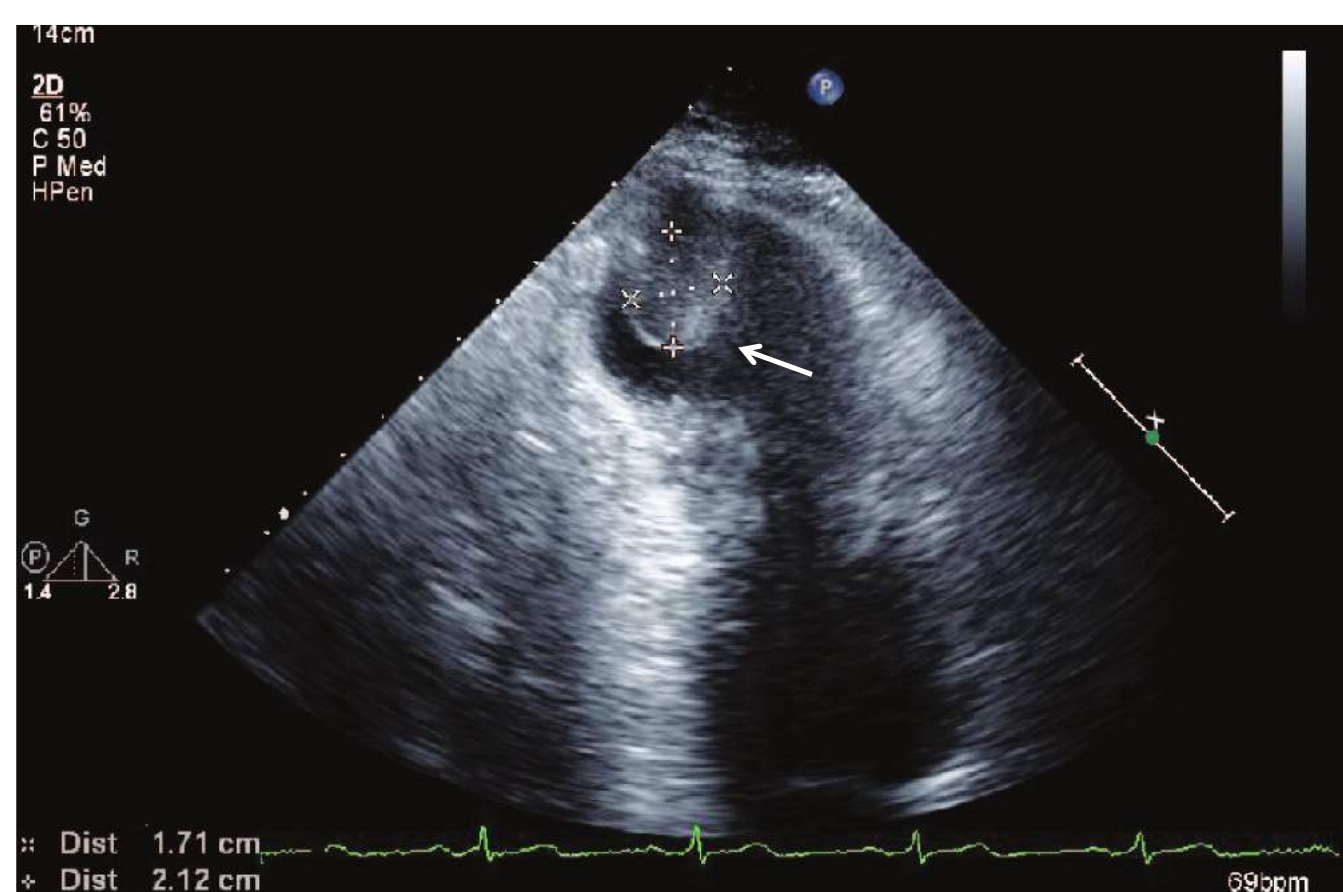


FIGURE 12-32

Cardiac thrombus (arrow) in an apical aneurysmal region following acute myocardial infarction.

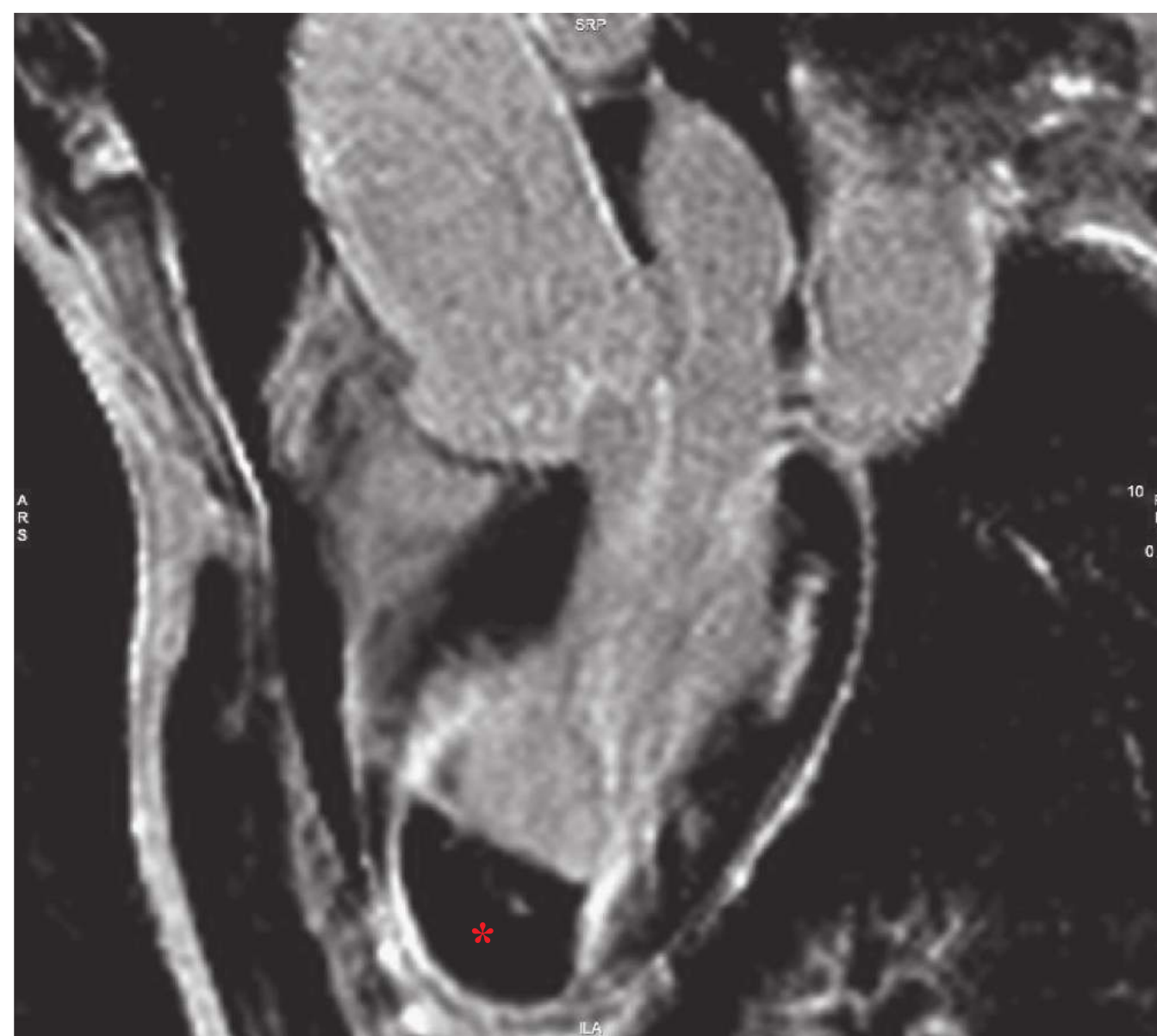


FIGURE 12-33

Late gadolinium enhancement image of a massive anterior infarction complicated by a dyskinetic left ventricular LV aneurysm and intracavitary thrombus (red asterisk).

information alone (**Fig. 12-33**). Comparing the signal intensities of a mass before and after contrast injection may confirm the lack of tissue vascularity (i.e., thrombus) by the lack of signal enhancement after contrast administration. Like intracardiac thrombus, regions of microvascular obstruction also appear dark, but microvascular obstruction is confined within the myocardium and surrounded by infarction and thus can be differentiated from intracardiac thrombus. CMR imaging for small thrombus in the left atrial appendage is difficult due to slow flow in the atrium and rhythm irregularity from atrial fibrillation, but it may be helpful in cases where transesophageal echocardiography is suboptimal or not feasible.

The majority of cardiac malignancy is metastatic, and metastatic cardiac malignancy is far more common than primary cardiac malignancies; these metastatic involvements of the heart are the result of direct invasion (e.g., lung and breast), lymphatic spread (e.g., lymphomas and melanomas), or hematogenous spread (e.g., renal cell carcinoma). Primary benign cardiac tumors are seen mostly in children and young adults and include atrial myxoma, rhabdomyoma, fibroma, and endocardial fibroelastoma (**Fig. 12-34**). Atrial myxomas are often seen as a round or multilobar mass in the left atrium (75%), right atrium (20%), or ventricles or mixed chambers (5%). They typically have inhomogeneous brightness in the center on cine steady-state free precession imaging due to their gelatinous contents and may have a pedunculated attachment to the fossa ovalis. Primary malignant cardiac tumors are extremely

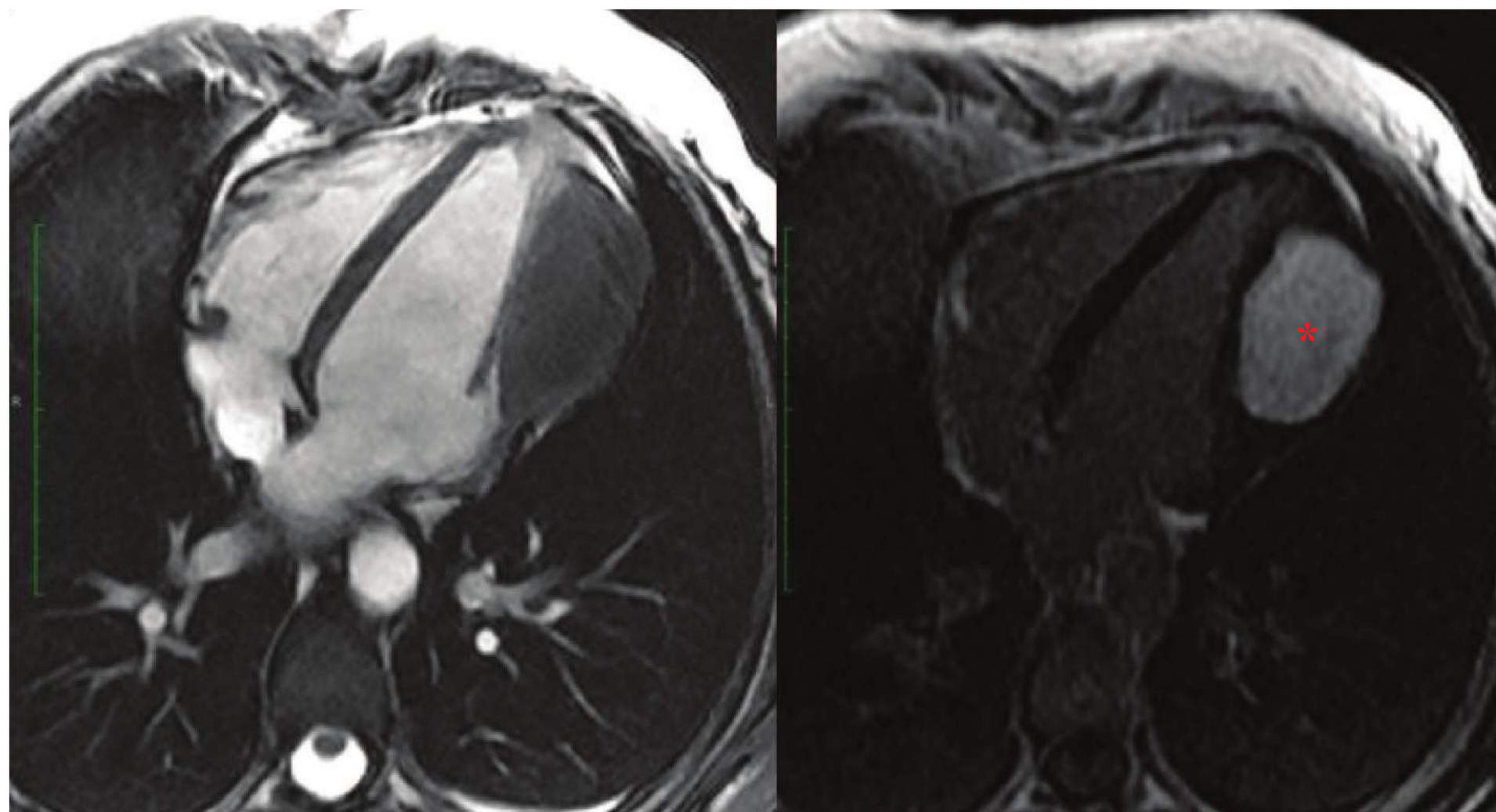


FIGURE 12-34

A case of a cardiac fibroma. A patient presented with shortness of breath and was found to have a large myocardial mass on echocardiography. Cine cardiac magnetic resonance imaging confirmed the large myocardial mass involving the anterolateral wall. Shortly after gadolinium contrast was injected, the myocardial mass demonstrated intense accumulation of contrast on LGE imaging (right panel, asterisk). This is a case of cardiac fibroma. The patient also has gingival hyperplasia and bifid thoracic ribs, a part of the rare Gorlin's syndrome.

rare and include angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma.

ROLE OF IMAGING IN INFECTIOUS AND INFLAMMATORY DISEASE

Patients with suspected endocarditis often undergo echocardiography for the purpose of identifying vegetations or intramyocardial abscesses. Vegetations are generally highly mobile structures that most typically are attached to valves or present in areas of the heart with turbulent flow. The absence of a vegetation on echocardiography does not rule out endocarditis, because small vegetations below the resolution of the imaging techniques can be present. Echocardiography remains the best technique for assessment of vegetations because its high temporal resolution allows visualization of the typical oscillating motion, although large vegetations can be visualized with other techniques (Fig. 12-35). The size and location of a vegetation do not necessarily provide any specific information about the type of infection. Abscesses, particularly around the aortic and mitral annuli, are particularly concerning in patients with endocarditis and should be suspected in patients with prolongation of cardiac intervals in the setting of endocarditis. Visualization of both vegetations

and possible abscesses is best done with transesophageal echocardiography, particularly in patients with prosthetic valves. Indeed, transesophageal echocardiography is the first test of choice in a patient with a mechanical mitral or aortic valve and suspected endocarditis (Fig. 12-35). Vegetations should be measured because their size has prognostic importance and can be used to decide whether a patient should be taken to surgery.

PET metabolic imaging is emerging as a potentially useful imaging technique to identify the source of infection in patients with prosthetic valves, vascular grafts, and implantable pacemakers/defibrillators, especially in patients in whom echocardiography and/or blood cultures are negative. There is an emerging literature documenting the potential value of macrophage-targeted metabolic imaging with ^{18}F -FDG and PET (Fig. 12-36). Likewise, FDG PET is also useful to identify vascular inflammation and monitor the response to immunosuppressive therapy (Fig. 12-37).

EVALUATION OF COMMON CONGENITAL ABNORMALITIES IN THE ADULT

While a discussion of complex congenital heart disease is beyond the scope of this chapter, a number of

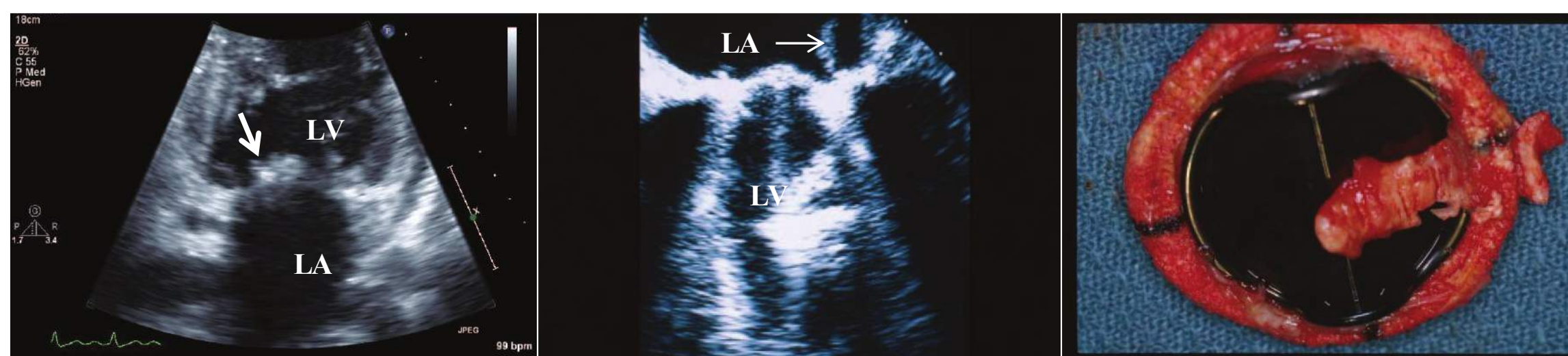


FIGURE 12-35

Vegetation on native mitral valve (left panel, arrow). Left atrium (LA) and left ventricle (LV) are indicated. Middle panel shows

a vegetation on a mechanical prosthesis (St. Jude) indicated by an arrow; right panel shows vegetation on prosthesis after excision.

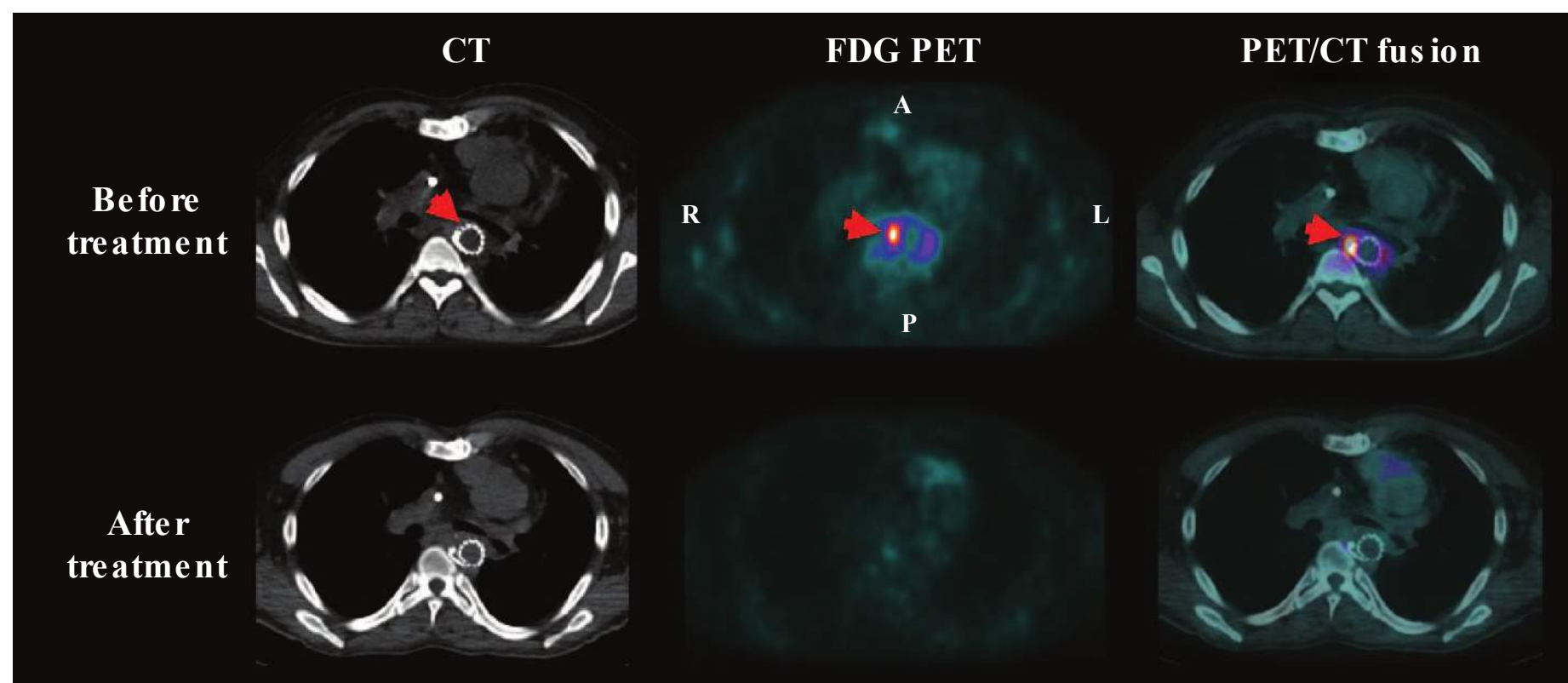


FIGURE 12-36

Representative cross-sectional computed tomography (CT; left), fluorodeoxyglucose (FDG) positron emission tomography (PET; middle), and fused CT and PET (right) images before and after antibiotic treatment in a patient with fever and suspected infection of the stent placed in the descending portion of the aortic arch (arrow) for treatment of aortic

coarctation. The FDG images before treatment demonstrate intense glucose uptake within the stent, consistent with inflammation/infection. The lower panel demonstrates significant attenuation of the FDG signal after treatment. (Images courtesy of Dr. Sharmila Dorbala, Brigham and Women's Hospital.)

common congenital abnormalities are present in adults, and cardiac imaging is essential to diagnosing and managing these conditions. Abnormalities of the interatrial septum probably represent the most common adult congenital cardiac abnormalities. Patent foramen ovale (PFO) can be identified in almost 25% of patients. In patients with PFO, a one-way flap in the region of the fossa ovalis is normally kept close by the left atrial pressure, which is generally higher than right atrial pressure for the majority of the cardiac cycle. However, right-to-left flow through a PFO can occur any time the right atrial pressure exceeds the left atrial pressure, including with maneuvers or conditions in which intrathoracic pressure is increased. The presence of a PFO can increase the likelihood of the paradoxical embolus, and thus the presence of a PFO should be determined in patients with stroke or systemic embolus of unknown etiology. Because the one-way flap of the PFO will be closed during much of the cardiac cycle, color flow

Doppler will usually not reveal a PFO. Instead, agitated saline (bubble study) is the best way to assess for PFO or atrial septal defect. Saline is agitated and injected peripherally and then enters the right atrium. If no shunt is present, only the right side of the heart will be pacified because the air bubbles will be too small to traverse the lungs. Because PFO is a one-way flap, maneuvers should be used to temporarily increase right atrial pressure. Either a Valsalva maneuver or sniff maneuver can be effective.

Atrial septal defects occur most commonly in the region of the fossa ovalis, referred to as secundum-type defects (**Fig. 12-38**). Additional atrial septal defects include defects of the sinus venosus and atrium primum. Color flow Doppler echocardiography is usually sufficient for diagnosis of a secundum-type atrial septal defect, but agitated saline is generally needed for the diagnosis of other types of atrial septal defects.

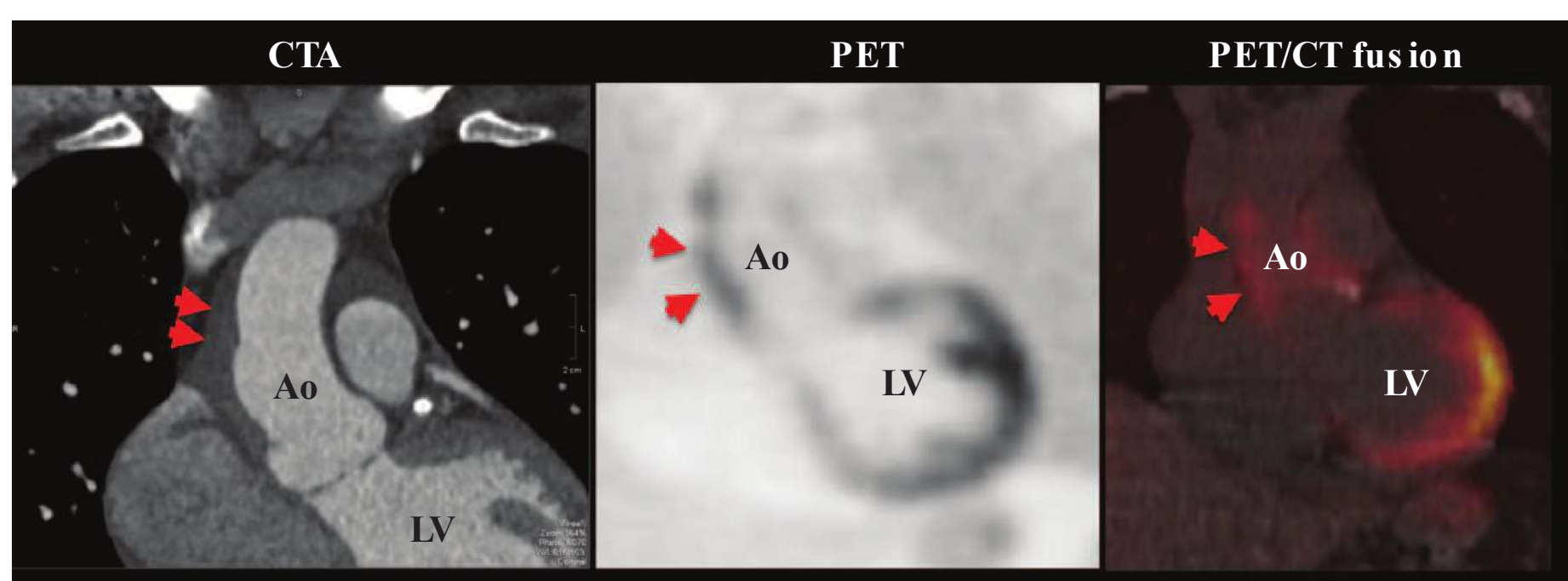


FIGURE 12-37

Representative coronal computed tomography (CT) angiographic (CTA; left panel), fluorodeoxyglucose (FDG) positron emission tomography (PET; middle panel), and fused CT and PET (right panel) images in a patient with

suspected aortitis. The CTA images demonstrate thickening of the ascending aorta (Ao), which correlates with intense, focal FDG uptake consistent with active inflammation. LV, left ventricle.

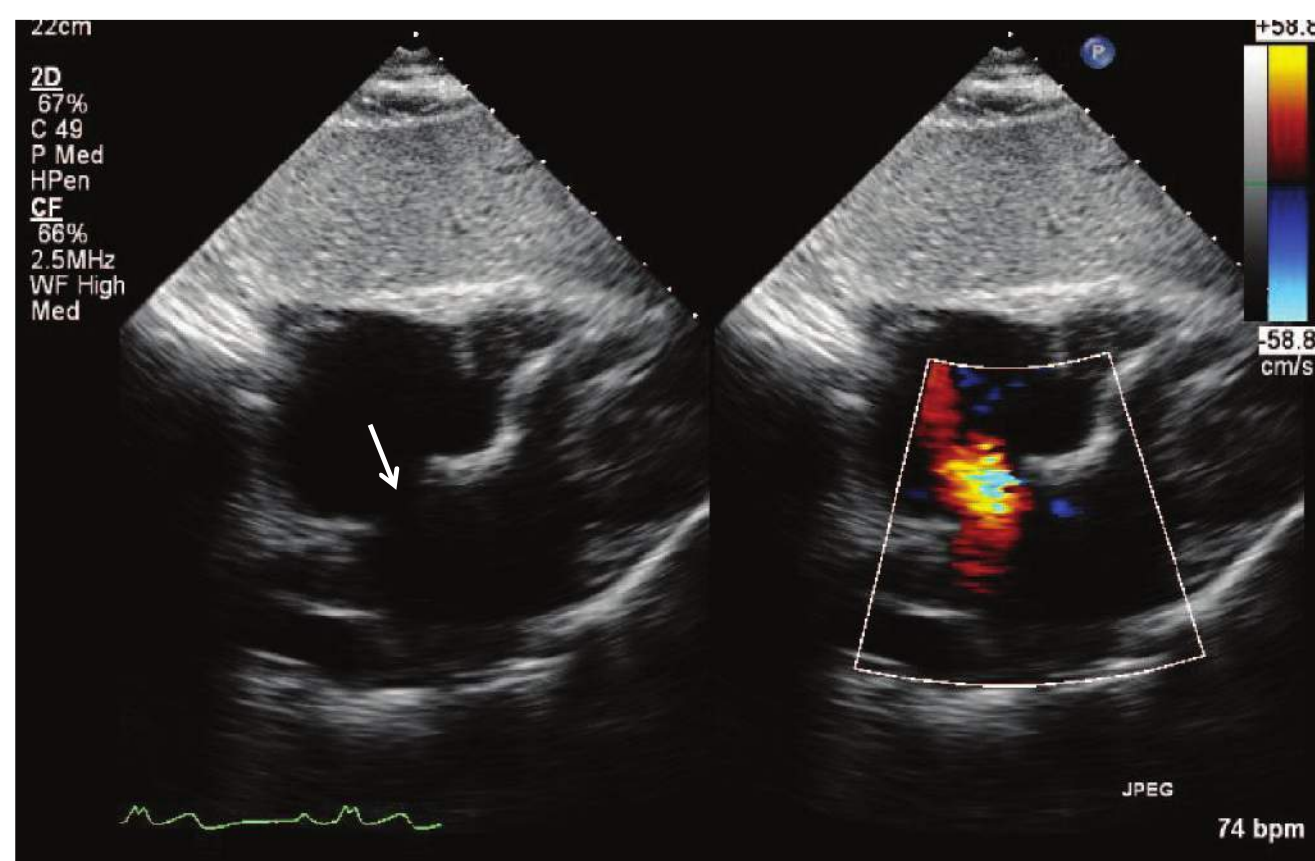


FIGURE 12-38

Large secundum-type atrial septal defect (arrow) noted in the subcostal view with color flow Doppler showing flow through the defect (right).

Ventricular septal defects can generally be visualized by color flow Doppler as turbulent high-velocity jets from the left to the right ventricle. In cases where the jet origin is unclear, continuous wave Doppler can estimate the velocities. These would be expected to be extremely high to reflect the pressure gradient between the left and right ventricles. Defects can occur in both the muscular and membranous portions of the ventricular septum.

In patients with either atrial or ventricular septal defects, estimation of the severity of the left-to-right shunt is essential and can be an important determinant in management decisions. Shunts are generally assessed by echocardiography by assessing the relationship between pulmonary flow and aortic flow, the Q_p/Q_s ratio. Shunts and cardiac anatomy of most congenital heart diseases can also be accurately evaluated by CMR (Fig. 12-39).

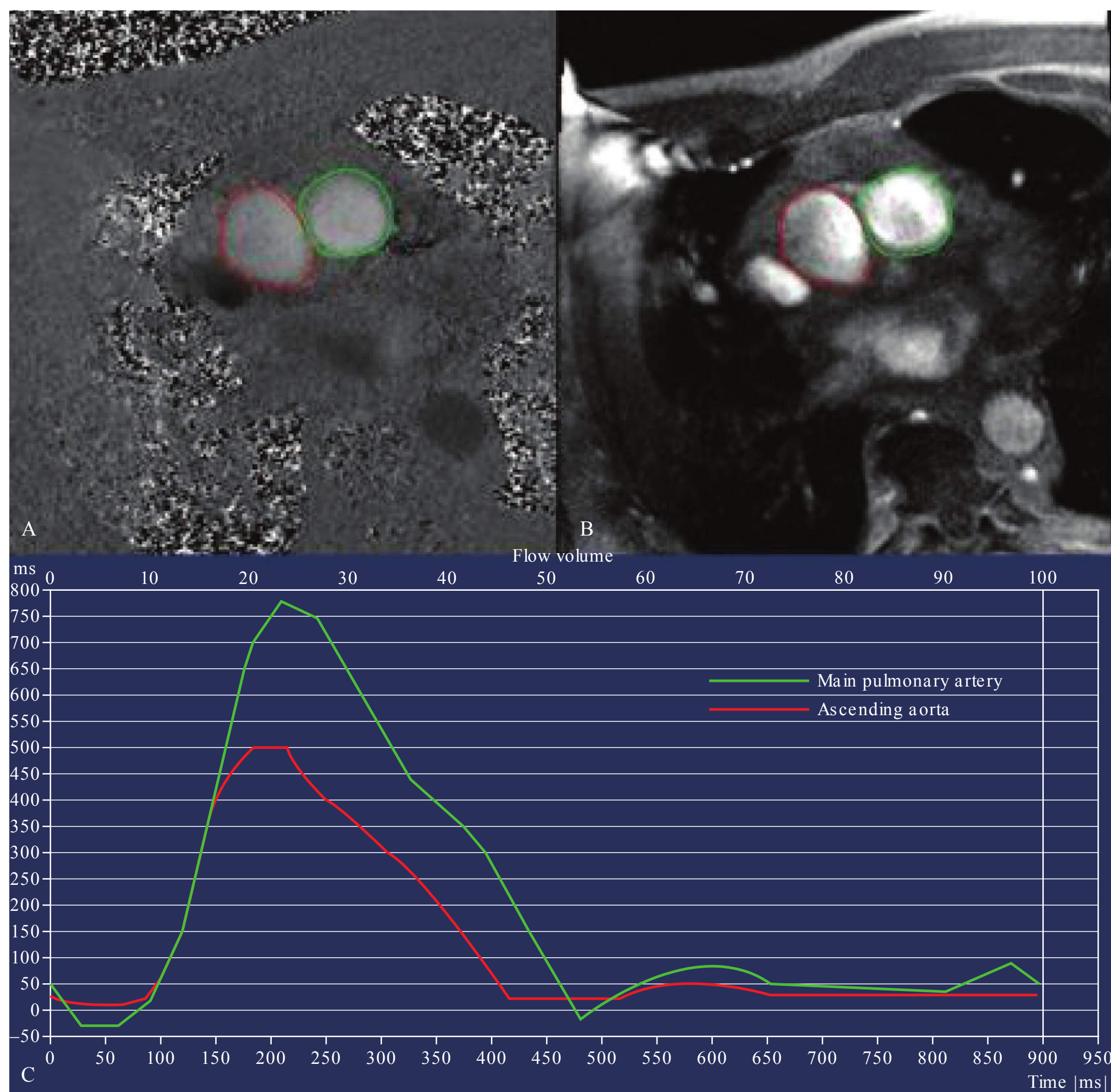


FIGURE 12-39

A and B are phase contrast images that display blood flow (phase images on A) and anatomy (structural images on B) of the aorta (red) and pulmonary artery (green). C demonstrates the flow curves of the aorta (red) and the pulmonary artery (green). Note that the total flow (area under the curve) was substantially higher

in the pulmonary artery than the aorta, indicative of a marked elevated pulmonary-to-systemic shunt ratio, as a result of the partial anomalous pulmonary venous return that drained into the superior vena cava.

Videos can be accessed via the following link:

<https://www.mhprofessional.com/mediacenter/>

VIDEO 12–1. Cine steady-state free precession (SSFP) imaging (left) in short axis in a patient who had a large anterior myocardial infarction.

Only one cut of a stack of short axis is shown. This method allows quantification of left ventricular (LV) and right ventricular (RV) volumes in diastole and systole and calculation of the LV ejection fraction, stroke volumes, and cardiac output (a product of LV stroke volume and heart rate). Note that in this case there is anterior and anteroseptal akinesia (lack of systolic wall thickening, as shown by the left cine movie, red arrows) matching by a near-transmural myocardial infarction as seen by the matching late gadolinium enhancement (LGE) image (right picture, white arrows).

VIDEO 12–2. Cardiac magnetic resonance (CMR) imaging of a patient in the long-axis four-chamber view.

Note that the basal aspect of the right ventricular (RV) free wall is thickened, aneurysmal, and akinetic (red arrows). The global RV systolic function is mildly reduced, and the RV is dilated. CMR can image the RV using tomographic views and can quantify the RV volumes and ejection fraction volumetrically. This is a patient who presented with syncopal spells and inducible ventricular tachycardia on subsequent workup. He was diagnosed to have arrhythmogenic right ventricular dysplasia.

VIDEO 12–3. Exercise echocardiogram showing rest images on left and poststress images on right, with parasternal long-axis, upper panel, and apical four-chamber, lower panel, end-systolic frames.

Following exercise, the distal septal/apical region becomes akinetic. A = upper left (UL); B = upper right (UR); C = lower left (LL); D = lower right (LR).

VIDEO 12–4. Cardiac magnetic resonance (CMR) myocardial perfusion imaging during vasodilating stress, in three parallel-short-axis views.

An bolus of gadolinium contrast was injected intravenously while rapid imaging acquisition occurred. The contrast enhances the right ventricle first, then travels through the pulmonary circulation, enters the left ventricle (LV), and then perfuses the LV myocardium. Myocardial perfusion defects with this technique show as black subendocardial rims, reflecting lack of contrast accumulation due to ischemia and/or scar. In this case, the anterior wall has a severe perfusion defect (red arrow). Figure 12-14 shows the late gadolinium enhancement (LGE) image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

VIDEO 12–5. A 60-year-old female presented with intermittent chest pain of 3 days in duration but was pain free at the time of assessment in the emergency room.

Admission electrocardiogram (ECG) demonstrated T-wave inversion in the anterior precordial lead, but cardiac enzymes were normal. A resting cardiac magnetic resonance (CMR) study reviewed a large area of anteroseptal hypokinesia (left picture, region of hypokinesia shown by the red arrows), matching with a large resting perfusion defect (middle picture, perfusion defect shown by the blue arrows). Late gadolinium enhancement (LGE) imaging (right picture), however, did not show any enhancement to indicate any infarction in the anteroseptal wall, suggesting that the hypokinesic and hypoperfused anteroseptal wall was viable. Urgent coronary angiography demonstrated an acute thrombus in the mid left anterior descending coronary artery, which required coronary stenting. This case represents an example of acute coronary syndrome with hibernating but viable myocardium in the anteroseptal wall. The anteroseptal wall recovered contractile function when reassessed 6 months later.

VIDEO 12–6. A patient with severe aortic regurgitation quantified by cardiac magnetic resonance (CMR).

Notice the dark flow jet during diastolic across the aortic valve. For quantitation of the aortic regurgitation severity, a cross-sectional cut was made just below the aortic valve, perpendicular to the aortic regurgitation jet, using phase contrast flow imaging. Apart from aortic regurgitation fraction and volume, CMR also can volumetrically quantify ventricular sizes and dimensions of the aorta, which are useful in monitoring patients with aortic valve diseases.

VIDEO 12–7. T2* Images of the heart (left panel) and the liver (right panel) of a patient who has hemochromatosis.

Note that iron and the liver are markedly darkened in these movies, indicating high load of iron in the heart muscle and liver. The rate of signal reduction (decay)

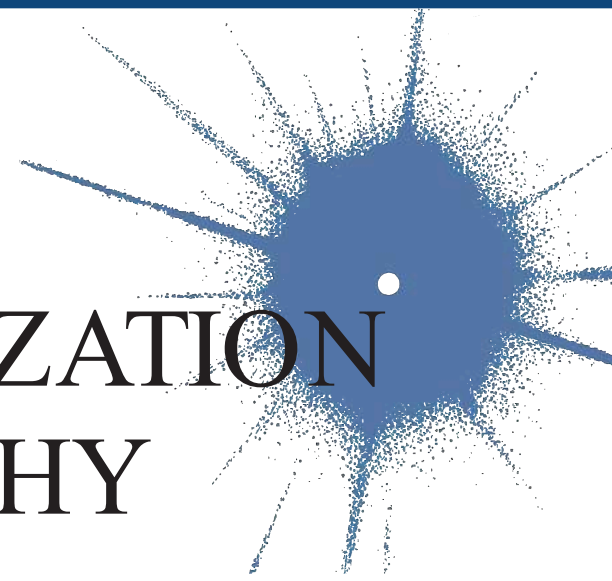
in the myocardium and liver can be calculated as T2* value expressed in milliseconds. In this case, the T2* was at 10 ms. T2* <20 ms in patients with cardiomyopathy has been shown to indicate iron toxicity as the etiology of the cardiomyopathy, and it carries prognostic value for such patients at risk of cardiac iron toxicity.

VIDEO 12–8. Shows the heart in long and short axis.

Note the large atria, thickened pericardium, and extensive pericardial adhesions. Given the extensive pericardial adhesions, there is little shearing motion of the ventricles against the parietal pericardium.

CHAPTER 13

DIAGNOSTIC CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY



Jane A. Leopold ■ David P. Faxon

Diagnostic cardiac catheterization and coronary angiography are considered the gold standard in the assessment of the anatomy and physiology of the heart and its associated vasculature. In 1929, Forssmann demonstrated the feasibility of cardiac catheterization in humans when he passed a urological catheter from a vein in his arm to his right atrium and documented the catheter's position in the heart by x-ray. In the 1940s, Cournand and Richards applied this technique to patients with cardiovascular disease to evaluate cardiac function. These three physicians were awarded the Nobel Prize in 1956. In 1958, Sones inadvertently performed the first selective coronary angiography when a catheter in the left ventricle slipped back across the aortic valve, engaged the right coronary artery, and power-injected 40 mL of contrast down the vessel. The resulting angiogram provided superb anatomic detail of the artery, and the patient suffered no adverse effects. Sones went on to develop selective coronary catheters, which were modified further by Judkins, who developed preformed catheters and allowed coronary artery angiography to gain widespread use as a diagnostic tool. In the United States, cardiac catheterization is the second most common operative procedure, with more than one million procedures performed annually.

CARDIAC CATHETERIZATION

INDICATIONS, RISKS, AND PREPROCEDURE MANAGEMENT

Cardiac catheterization and coronary angiography are indicated to evaluate the extent and severity of cardiac disease in symptomatic patients and to determine if medical, surgical, or catheter-based interventions are warranted (**Table 13-1**). They are also used to exclude

severe disease in symptomatic patients with equivocal findings on noninvasive studies and in patients with chest-pain syndromes of unclear etiology for whom a definitive diagnosis is necessary for management. Cardiac catheterization is not mandatory prior to cardiac surgery in some younger patients who have congenital or valvular heart disease that is well defined by noninvasive imaging and who do not have symptoms or risk factors that suggest concomitant coronary artery disease.

The risks associated with elective cardiac catheterization are relatively low, with a reported risk of 0.05% for myocardial infarction, 0.07% for stroke, and 0.08–0.14% for death. These risks increase substantially if the catheterization is performed emergently, during acute myocardial infarction or in hemodynamically unstable patients. Additional risks of the procedure include tachy- or bradyarrhythmias that require countershock or pharmacologic therapy, acute renal failure leading to transient or permanent dialysis, vascular complications that necessitate surgical repair, and significant access-site bleeding. Of these risks, vascular access-site bleeding is the most common complication, occurring in 1.5–2.0% of patients, with major bleeding events associated with a worse short- and long-term outcome.

In patients who understand and accept the risks associated with cardiac catheterization, there are no absolute contraindications when the procedure is performed in anticipation of a life-saving intervention. Relative contraindications do, however, exist; these include decompensated congestive heart failure; acute renal failure; severe chronic renal insufficiency, unless dialysis is planned; bacteremia; acute stroke; active gastrointestinal bleeding; severe, uncorrected electrolyte abnormalities; a history of an anaphylactic/anaphylactoid reaction to iodinated contrast agents; and a history of allergy/bronchospasm to aspirin in patients for whom progression to

TABLE 13-1
INDICATIONS FOR CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY

Coronary Artery Disease
Asymptomatic or Symptomatic
High risk for adverse outcome based on noninvasive testing
Sudden cardiac death
Sustained (>30 s) monomorphic ventricular tachycardia
Nonsustained (<30 s) polymorphic ventricular tachycardia
Symptomatic
Canadian Cardiology Society Class II, III, or IV stable angina on medical therapy
Acute coronary syndrome (unstable angina and non-ST-segment elevation myocardial infarction)
Chest-pain syndrome of unclear etiology and equivocal findings on noninvasive tests
ST-Segment Elevation Acute Myocardial Infarction
Reperfusion with primary percutaneous coronary intervention
Persistent or recurrent ischemia
Pulmonary edema and/or reduced ejection fraction
Cardiogenic shock or hemodynamic instability
Risk stratification or positive stress test after acute myocardial infarction
Mechanical complications—mitral regurgitation, ventricular septal defect
Valvular Heart Disease
Suspected severe valve disease in symptomatic patients—dyspnea, angina, heart failure, syncope
Infective endocarditis with need for cardiac surgery
Asymptomatic patients with aortic regurgitation and cardiac enlargement or a ejection fraction
Prior to cardiac surgery in patients with suspected coronary artery disease
Congestive Heart Failure
New onset with angina or suspected undiagnosed coronary artery disease
New-onset cardiomyopathy of uncertain cause or suspected to be due to coronary artery disease
Congenital Heart Disease
Prior to surgical correction, when symptoms or noninvasive testing suggests coronary disease
Suspicion for congenital coronary anomalies
Pericardial Disease
Symptomatic patients with suspected cardiac tamponade or constrictive pericarditis
Cardiac Transplantation
Preoperative and postsurgical evaluation
Other Conditions
Hypertrophic cardiomyopathy with angina
Diseases of the aorta when knowledge of coronary artery involvement is necessary for management

a percutaneous coronary intervention is likely and aspirin desensitization has not been performed.

Contrast allergy and contrast-induced acute kidney injury merit further consideration, because these adverse

events may occur in otherwise healthy individuals and prophylactic measures exist to reduce risk. Allergic reactions to contrast agents occur in <5% of cases, with severe anaphylactoid (clinically indistinguishable from anaphylaxis, but not mediated by an IgE mechanism) reactions occurring in 0.1%–0.2% of patients. Mild reactions manifest as nausea, vomiting, and urticaria, while severe anaphylactoid reactions lead to hypotensive shock, pulmonary edema, and cardiorespiratory arrest. Patients with a history of significant contrast allergy should be premedicated with corticosteroids and antihistamines (H₁- and H₂-blockers) and studies performed with non-ionic, low-osmolar contrast agents that have a lower reported rate of allergic reactions.

Contrast-induced acute kidney injury, defined as an increase in creatinine >0.5 mg/dL or 25% above baseline that occurs 48–72 hours after contrast administration, occurs in ~2–7% of patients with rates of 20–30% reported in high-risk patients, including those with diabetes mellitus, congestive heart failure, chronic kidney disease, anemia, and older age. Dialysis is required in 0.3–0.7% of patients and is associated with a fivefold increase in in-hospital mortality. For all patients, adequate intravascular volume expansion with intravenous 0.9% saline (1.0–1.5 mL/kg per hour) for 3–12 hours before and continued 6–24 hours after the procedure limits the risk of contrast-induced acute kidney injury. Pretreatment with N-acetylcysteine (Mucomyst) has not reduced the risk of contrast-induced acute kidney injury consistently and, therefore, is no longer recommended routinely. Diabetic patients treated with metformin should stop the drug 48 hours prior to the procedure to limit the associated risk of lactic acidosis. Other strategies to decrease risk include the administration of sodium bicarbonate (3 mL/kg per hour) 1 hour before and 6 hours after the procedure; use of low- or iso-osmolar contrast agents; and limiting the volume of contrast to <100 mL per procedure.

Cardiac catheterization is performed after the patient has fasted for 6 hours and has received intravenous conscious sedation to remain awake but sedated during the procedure. All patients with suspected coronary artery disease are pretreated with 325 mg aspirin. In patients in whom the procedure is likely to progress to a percutaneous coronary intervention, an additional antiplatelet agent should be started: clopidogrel (600-mg loading dose and 75 mg daily) or prasugrel (60-mg loading dose and 10 mg daily), or ticagrelor (180-mg loading and 90 mg twice daily). Prasugrel should not be selected for individuals with prior stroke or transient ischemic attack. Warfarin is held starting 2–3 days prior to the catheterization to allow the international normalized ratio (INR) to fall to <1.7 and limit access-site bleeding complications. Cardiac catheterization is a sterile procedure, so antibiotic prophylaxis is not required.

TECHNIQUE

Cardiac catheterization and coronary angiography provide a detailed hemodynamic and anatomic assessment of the heart and coronary arteries. The selection of procedures is dependent on the patient's symptoms and clinical condition, with some direction provided by noninvasive studies.

Vascular access

Cardiac catheterization procedures are performed using a percutaneous technique to enter the femoral artery and vein as the preferred access sites for left and right heart catheterization, respectively. A flexible sheath is inserted into the vessel over a guidewire, allowing diagnostic catheters to be introduced into the vessel and advanced toward the heart using fluoroscopic guidance. The radial artery (or brachial artery) may also be used as an arterial access site in patients, particularly those with peripheral arterial disease that involves the abdominal aorta, iliac, or femoral vessels; severe iliac artery tortuosity; morbid obesity; or preference for early postprocedure ambulation. Use of radial-artery access is gaining popularity due to a lower rate of access-site bleeding complications. A normal Allen's test confirming dual blood supply to the hand from the radial and ulnar arteries is recommended prior to access at this site. The internal jugular or antecubital veins serve as alternate access sites to the right heart when the patient has an inferior vena cava filter in place or requires prolonged hemodynamic monitoring.

Right heart catheterization

This procedure measures pressures in the right heart. Right heart catheterization is no longer a routine part of diagnostic cardiac catheterization, but it is reasonable in patients with unexplained dyspnea, valvular heart disease, pericardial disease, right and/or left ventricular dysfunction, congenital heart disease, and suspected intracardiac shunts. Right heart catheterization uses a balloon-tipped flotation catheter that is advanced sequentially to the right atrium, right ventricle, pulmonary artery, and pulmonary wedge position (as a surrogate for left atrial pressure) using fluoroscopic guidance; in each cardiac chamber, pressure is measured and blood samples are obtained for oxygen saturation analysis to screen for intracardiac shunts.

Left heart catheterization

This procedure measures pressures in the left heart as a determinant of left ventricular performance. With the aid of fluoroscopy, a catheter is guided to the ascending aorta and across the aortic valve into the left ventricle to provide a direct measure of left ventricular pressure. In patients with a tilting-disc prosthetic aortic valve, crossing the valve with a catheter is contraindicated, and the

left heart may be accessed via a transseptal technique from the right atrium using a needle-tipped catheter to puncture the atrial septum at the fossa ovalis. Once the catheter crosses from the right to the left atrium, it can be advanced across the mitral valve to the left ventricle. This technique is also used for mitral valvuloplasty. Heparin is given for prolonged procedures to limit the risk of stroke from embolism of clots that may form on the catheter. For patients with heparin-induced thrombocytopenia, the direct thrombin inhibitors bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of the procedure) or argatroban (350 µg/kg bolus, 15 µg/kg per minute for the duration of the procedure) may be used.

HEMODYNAMICS

A comprehensive hemodynamic assessment involves obtaining pressure measurements in the right and left heart and peripheral arterial system and determining the cardiac output (**Table 13-2**). The shape

TABLE 13-2

NORMAL VALUES FOR HEMODYNAMIC MEASUREMENTS

PRESSURES (mm Hg)

Right atrium	
Mean	0–5
a wave	1–7
v wave	1–7
Right ventricle	
Peak systolic/end diastolic	17–32/1–7
Pulmonary artery	
Peak systolic/end diastolic	17–32/1–7
Mean	9–19
Pulmonary capillary wedge (mean)	4–12
Left atrium	
Mean	4–12
a wave	4–15
v wave	4–15
Left ventricle	
Peak systolic/end diastolic	90–130/5–12
Aorta	
Peak systolic/end diastolic	90–130/60–85
Mean	70–100
(Resistances [dyn·s]/cm ⁵)	
Systemic vascular resistance	900–1400
Pulmonary vascular resistance	40–120
Oxygen Consumption Index ([L·min]/m ²)	115–140
Arteriovenous oxygen difference (vol %)	3.5–4.8
Cardiac index ([L·min]/m ²)	2.8–4.2

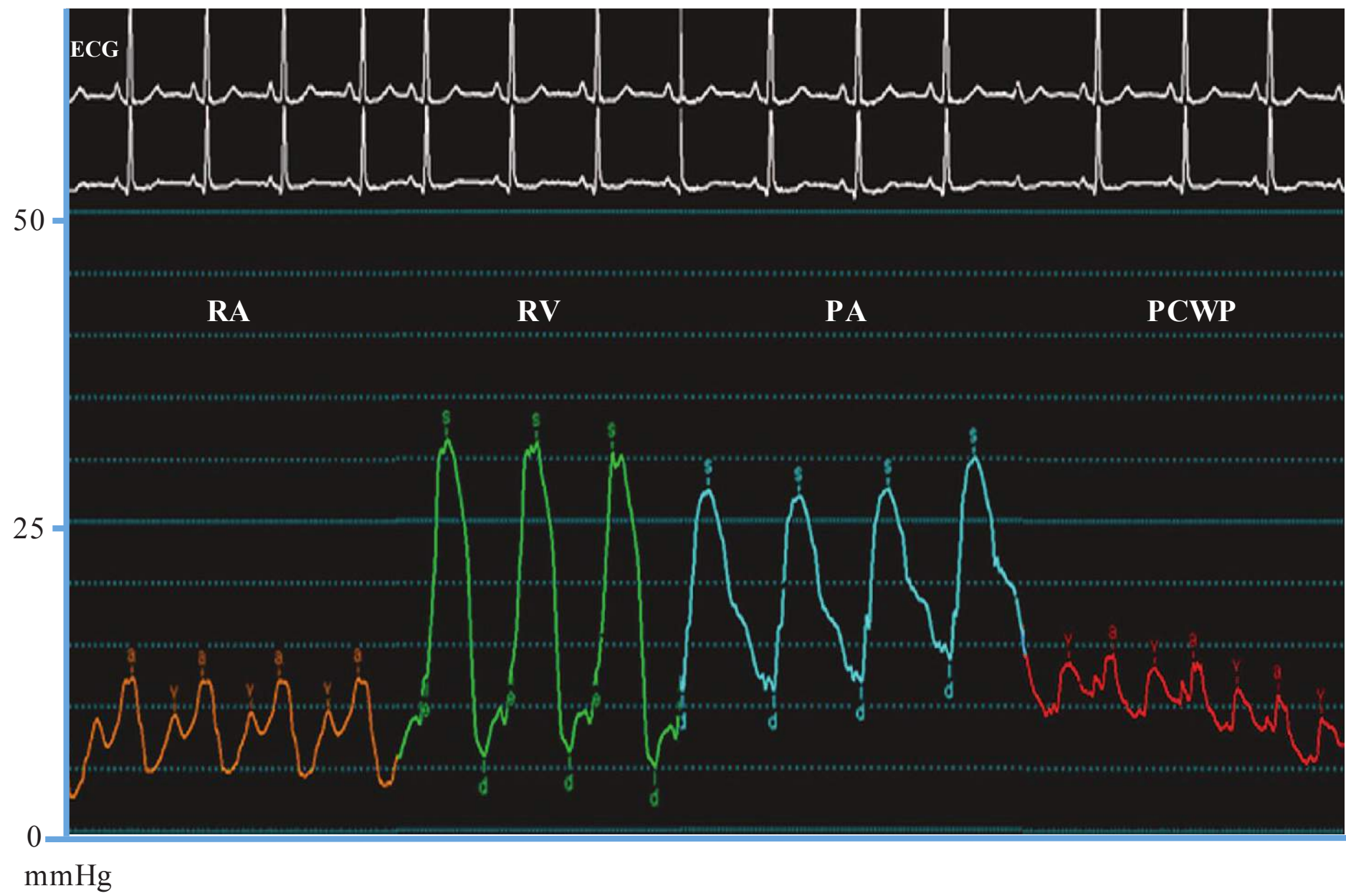


FIGURE 13-1
Normal hemodynamic waveforms recorded during right heart catheterization. Atrial pressure tracings have a characteristic “a” wave that reflects atrial contraction and a “v” wave that reflects pressure changes in the atrium during ventricular systole.

Ventricular pressure tracings have a low-pressure diastolic filling period and a sharp rise in pressure that occurs during ventricular systole. d, diastole; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle; s, systole.

and magnitude of the pressure waveforms provide important diagnostic information; an example of normal pressure tracings is shown in **Fig. 13-1**. In the absence of valvular heart disease, the atria and ventricles are “one chamber” during diastole when the tricuspid and mitral valves are open while in systole, when the pulmonary and aortic valves are open, the ventricles and their respective outflow tracts are considered “one chamber.” These concepts form the basis

by which hemodynamic measurements are used to assess valvular stenosis. When aortic stenosis is present, there is a systolic pressure gradient between the left ventricle and the aorta; when mitral stenosis is present, there is a diastolic pressure gradient between the pulmonary capillary wedge (left atrial) pressure and the left ventricle (**Fig. 13-2**). Hemodynamic measurements also discriminate between aortic stenosis and hypertrophic obstructive cardiomyopathy where

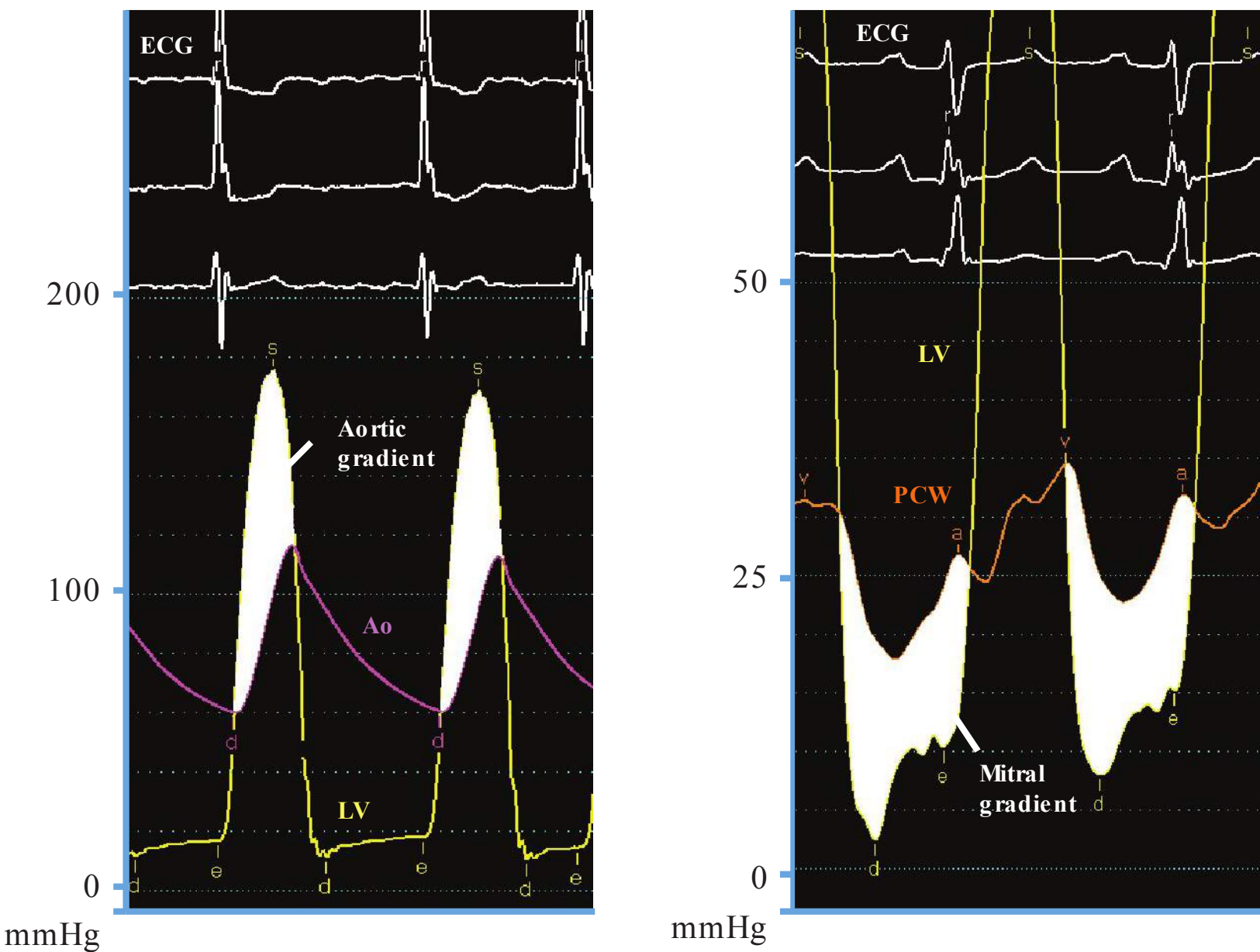


FIGURE 13-2
Severe aortic and mitral stenosis. Simultaneous recording of left ventricular (LV) and aortic (Ao) pressure tracings demonstrates a 62-mmHg mean systolic gradient (shaded area) that corresponds to an aortic valve area of 0.6 cm² (left). Simultaneous recording of LV and pulmonary capillary wedge (PCW) pressure tracings reveals a 14-mmHg mean diastolic gradient (shaded area) that is consistent with critical mitral stenosis (mitral valve area = 0.5 cm²). d, diastole; e, end diastole; s, systole.

the asymmetrically hypertrophied septum creates a dynamic intraventricular pressure gradient during ventricular systole. The magnitude of this obstruction is measured using an end-hole catheter positioned at the left ventricular apex that is pulled back while recording pressure; once the catheter has passed the septal obstruction and is positioned in the apex of the left ventricle, a gradient can be measured between the left ventricular apex and the aorta. Hypertrophic obstructive cardiomyopathy is confirmed by the Brockenbrough-Braunwald sign: following a premature ventricular contraction, there is an increase in the left ventricular–aorta pressure gradient with a simultaneous decrease in the aortic pulse pressure. These findings are absent in aortic stenosis.

Regurgitant valvular lesions increase volume (and pressure) in the “receiving” cardiac chamber. In severe mitral and tricuspid regurgitation, the increase in blood flow to the atria takes place during ventricular systole, leading to an increase in the v wave (two times greater than the mean pressure). Severe aortic regurgitation leads to a decrease in aortic diastolic pressure with a concomitant rise in left ventricular end-diastolic pressure, resulting in equalization of pressures between the two chambers at end-diastole.

Hemodynamic measurements are also used to differentiate between cardiac tamponade, constrictive pericarditis, and restrictive cardiomyopathy (Table 13-3). In cardiac tamponade, right atrial pressure is increased with a decreased or absent “y” descent, indicative of impaired right atrial emptying in diastole, and there is diastolic equalization of pressures in all cardiac chambers. In constrictive pericarditis, right atrial pressure is elevated with a prominent “y” descent, indicating rapid filling of the right ventricle during early diastole. A diastolic dip and plateau or “square root sign,” in the ventricular waveforms due to an abrupt halt in ventricular filling during diastole; right ventricular and pulmonary artery pressures are elevated; and discordant pressure changes in the right and left ventricles with inspiration (right ventricular systolic pressure increases while left ventricular systolic pressure decreases) are observed. The latter hemodynamic phenomenon is the most specific for constriction. Restrictive cardiomyopathy may be distinguished from constrictive pericarditis by a marked increase in right ventricular and pulmonary artery systolic pressures (usually >60 mmHg), a separation of the left and right ventricular diastolic pressures by >5 mmHg (at baseline or with acute volume loading), and concordant changes in left and right ventricular diastolic filling pressures with inspiration (both increase).

TABLE 13-3

HEMODYNAMIC FINDINGS IN TAMPONADE, CONSTRICTIVE PERICARDITIS, AND RESTRICTIVE CARDIOMYOPATHY

	CARDIAC TAMPONADE	CONSTRICTIVE PERICARDITIS	EFFUSIVE-CONSTRICTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY
Pericardial pressure	↑	↑	↑	Normal
Right atrium pressure	↑	↑	↑ (Fails to decrease by 50% or to <10 mmHg after pericardiocentesis)	↑
Right atrium pressure waveform	Prominent “x” descent Diminished or absent “y” descent	Prominent “x” descent Prominent “y” descent	Prominent “x” descent “y” descent less prominent than expected	Prominent “y” descent
Right ventricle systolic pressure	<50 mmHg	<50 mmHg	<50 mmHg	>60 mmHg
Right ventricle end-diastolic pressure	Equals left ventricular end-diastolic pressure within 5 mmHg	>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	<1/3 right ventricular systolic pressure Less than left ventricular end-diastolic pressure by ≥ 5 mmHg
Right ventricle pressure waveform		Dip and plateau or “square root” sign	Dip and plateau or “square root” sign	Dip and plateau or “square root” sign
Right ventricle–left ventricle systolic pressure relationship with inspiration	Discordant	Discordant	Discordant	Concordant

Cardiac output

Cardiac output is measured by the Fick method or the thermodilution technique. Typically, the Fick method and thermodilution technique are both performed during cardiac catheterization, although the Fick method is considered more reliable in the presence of tricuspid regurgitation and in low-output states. The Fick method uses oxygen as the indicator substance and is based on the principle that the amount of a substance taken up or released by an organ (oxygen consumption) is equal to the product of its blood flow (cardiac output) and the difference in the concentration of the substance in the arterial and venous circulation (arterial-venous oxygen difference). Thus, the formula for calculating the Fick cardiac output is:

$$\text{Cardiac output (L/min)} = \frac{\text{oxygen consumption [mL/min]}}{\text{arterial-venous oxygen difference [mL/L]}}$$

Oxygen consumption is estimated as 125 mL oxygen/minute $\times$ body surface area, and the arterial-venous oxygen difference is determined by first calculating the oxygen carrying capacity of blood (hemoglobin [g/100 mL] $\times$ 1.36 [mL oxygen/g hemoglobin] $\times$ 10) and multiplying this product by the fractional oxygen saturation. The thermodilution method measures a substance that is injected into and adequately mixes with blood. In contemporary practice, thermodilution cardiac outputs are measured using temperature as the indicator. Measurements are made with a thermistor-tipped catheter that detects temperature deviations in the pulmonary artery after the injection of 10 mL of room-temperature normal saline into the right atrium.

Vascular resistance

Resistance across the systemic and pulmonary circulations is calculated by extrapolating from Ohm's law of electrical resistance and is equal to the mean pressure gradient divided by the mean flow (cardiac output). Therefore, systemic vascular resistance is ([mean aortic pressure – mean right atrial pressure]/cardiac output) multiplied by 80 to convert the resistance from Wood units to dyn-cm⁻⁵. Similarly, the pulmonary vascular resistance is ([mean pulmonary artery – mean pulmonary capillary wedge pressure]/cardiac output) $\times$ 80. Pulmonary vascular resistance is lowered by oxygen, nitroprusside, calcium channel blockers, prostacyclin infusions, and inhaled nitric oxide; these therapies may be administered during catheterization to determine if increased pulmonary vascular resistance is fixed or reversible.

Valve area

Hemodynamic data may also be used to calculate the valve area using the Gorlin formula that equates the area to the flow across the valve divided by the pressure

gradient between the cardiac chambers surrounding the valve. The formula for the assessment of valve area is: Area = (cardiac output [cm³/min]/[systolic ejection period or diastolic filling period][heart rate])/44.3 C $\times$ square root of the pressure gradient, where C = 1 for aortic valve and 0.85 for the mitral valve. A valve area of <1.0 cm² and a mean gradient of greater than 40 mmHg indicate severe aortic stenosis, while a valve area of <1.5 cm² and a mean gradient >5–10 mmHg is consistent with moderate-to-severe mitral stenosis; in symptomatic patients with a mitral valve area >1.5 cm², a mean gradient >15 mmHg, pulmonary artery pressure >60 mmHg, or a pulmonary artery wedge pressure >25 mmHg after exercise is also considered significant and may warrant intervention. The modified Hakki formula has also been used to estimate aortic valve area. This formula calculates the valve area as the cardiac output (L/min) divided by the square root of the pressure gradient. Aortic valve area calculations based on the Gorlin formula are flow-dependent and, therefore, for patients with low cardiac outputs, it is imperative to determine if a decreased valve area actually reflects a fixed stenosis or is overestimated by a low cardiac output and stroke volume that is insufficient to open the valve leaflets fully. In these instances, cautious hemodynamic manipulation using dobutamine to increase the cardiac output and recalculation of the aortic valve area may be necessary.

Intracardiac shunts

In patients with congenital heart disease, detection, localization, and quantification of the intracardiac shunt should be evaluated. A shunt should be suspected when there is unexplained arterial desaturation or increased oxygen saturation of venous blood. A “step up” or increase in oxygen content indicates the presence of a left-to-right shunt while a “step down” indicates a right-to-left shunt. The shunt is localized by detecting a difference in oxygen saturation levels of 5–7% between adjacent cardiac chambers. The severity of the shunt is determined by the ratio of pulmonary blood flow (Q_p) to the systemic blood flow (Q_s), or Q_p/Q_s = ([systemic arterial oxygen content – mixed venous oxygen content]/pulmonary vein oxygen content – pulmonary artery oxygen content). For an atrial septal defect, a shunt ratio of 1.5 is considered significant and factored with other clinical variables to determine the need for intervention. When a congenital ventricular septal defect is present, a shunt ratio of ≥ 2.0 with evidence of left ventricular volume overload is a strong indication for surgical correction.

VENTRICULOGRAPHY AND AORTOGRAPHY

Ventriculography to assess left ventricular function may be performed during cardiac catheterization. A

pigtail catheter is advanced retrograde across the aortic valve into the left ventricle and 30–45 mL of contrast is power-injected to visualize the left ventricular chamber during the cardiac cycle. The ventriculogram is usually performed in the right anterior oblique projection to examine wall motion and mitral valve function. Normal wall motion is observed as symmetric contraction of all segments; hypokinetic segments have decreased contraction, akinetic segments do not contract, and dyskinetic segments appear to bulge paradoxically during systole (Fig. 13-3). Ventriculography may also reveal a left ventricular aneurysm, pseudoaneurysm, or diverticulum and can be used to assess mitral valve prolapse and the severity of mitral regurgitation. The degree of mitral regurgitation is estimated by comparing the density of contrast opacification of the left atrium with that of the left ventricle. Minimal contrast reflux into the left atrium is considered 1+ mitral regurgitation, while contrast density in the left atrium that is greater than that in the left ventricle with reflux of contrast into the pulmonary veins within three beats defines 4+ mitral regurgitation. Ventriculography performed in the left anterior oblique projection can be used to identify a ventricular septal defect. Calculation of the ventricular volumes in systole and diastole allows calculation of stroke volume and cardiac output.

Aortography in the cardiac catheterization laboratory visualizes abnormalities of the ascending aorta,

including aneurysmal dilation and involvement of the great vessels, as well as dissection with compression of the true lumen by an intimal flap that separates the true and false lumina. Aortography can also be used to identify patent saphenous vein grafts that elude selective cannulation, identify shunts that involve the aorta such as a patent ductus arteriosus, and provide a qualitative assessment of aortic regurgitation using a 1+–4+ scale similar to that used for mitral regurgitation.

CORONARY ANGIOGRAPHY

Selective coronary angiography is almost always performed during cardiac catheterization and is used to define the coronary anatomy and determine the extent of epicardial coronary artery and coronary artery bypass graft disease. Specially shaped coronary catheters are used to engage the left and right coronary ostia. Hand injection of radiopaque contrast agents creates a coronary “luminogram” that is recorded as radiographic images (cine angiography). Because the coronary arteries are three-dimensional objects that are in motion with the cardiac cycle, angiograms of the vessels using several different orthogonal projections are taken to best visualize the vessels without overlap or foreshortening.

The normal coronary anatomy is highly variable between individuals, but, in general, there are two

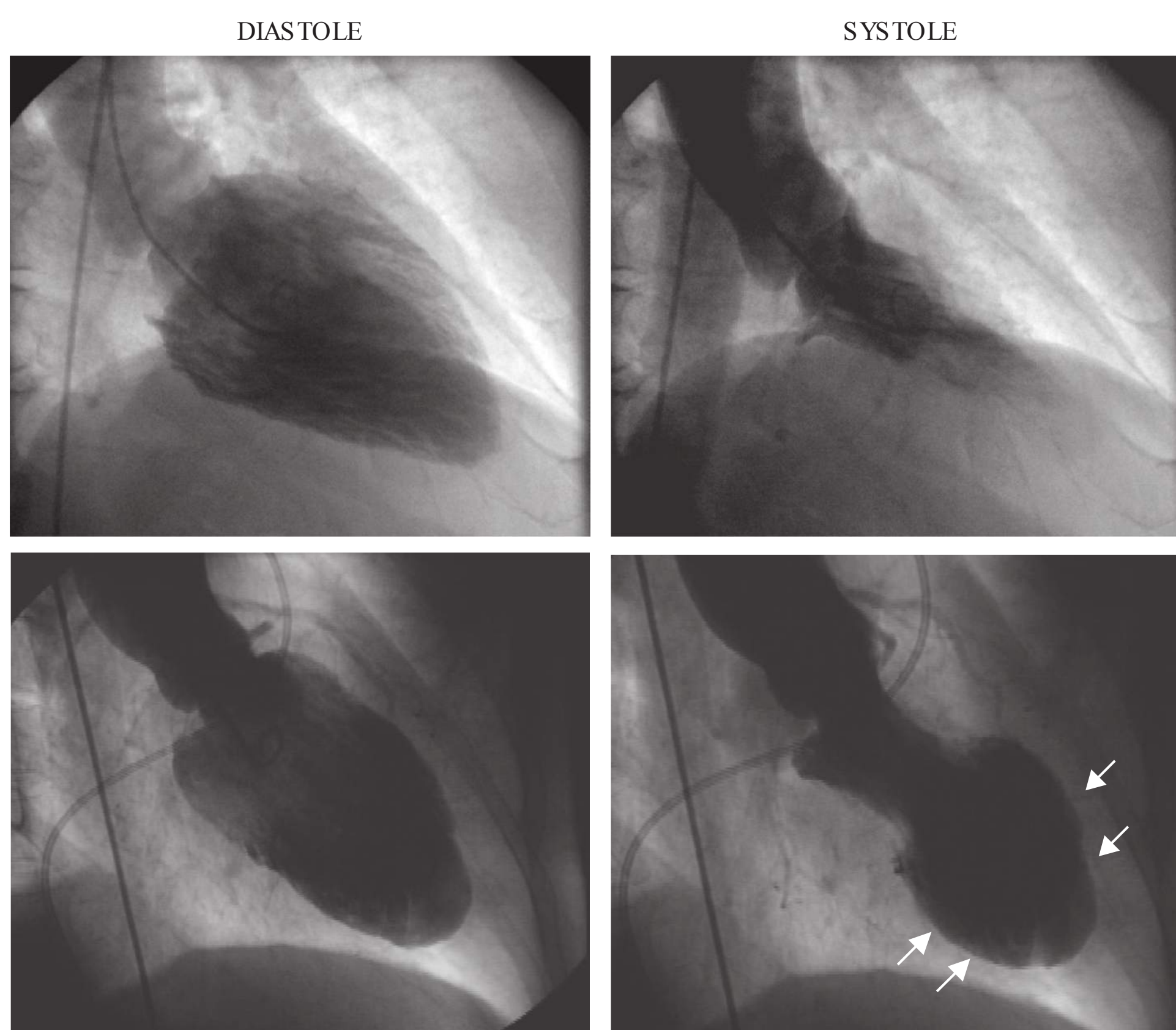


FIGURE 13-3

Left ventriculogram at end diastole (left) and end systole (right). In patients with normal left ventricular function, the ventriculogram reveals symmetric contraction of all walls (top). Patients with coronary artery disease may have wall motion abnormalities on ventriculography as seen in this 60-year-old male following a large anterior myocardial infarction. In systole, the anterior, apical, and inferior walls are akinetic (white arrows) (bottom).

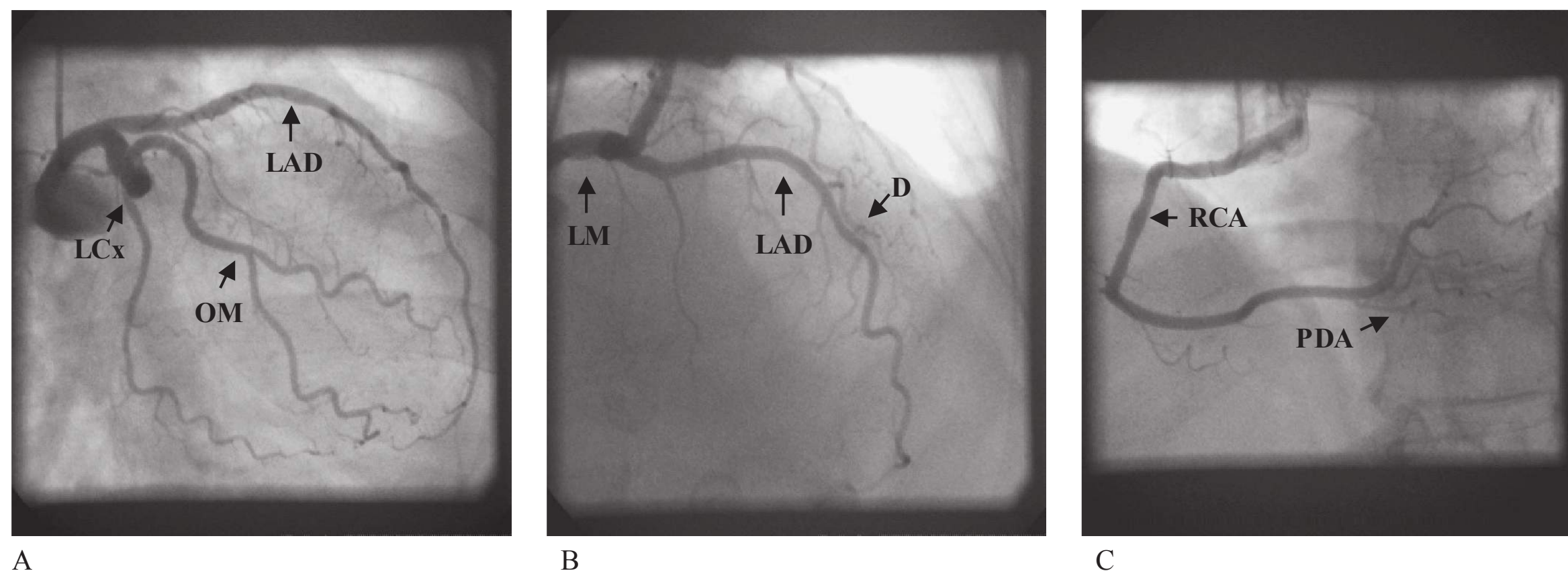


FIGURE 13-4

Normal coronary artery anatomy. A. Coronary angiogram showing the left circumflex (LCx) artery and its obtuse marginal (OM) branches. The left anterior descending artery (LAD) is also seen but may be foreshortened in this view. B. The LAD and its

diagonal (D) branches are best seen in cranial views. In this angiogram, the left main (LM) coronary artery is also seen. C. The right coronary artery (RCA) gives off the posterior descending artery (PDA), so this is a right dominant circulation.

coronary ostia and three major coronary vessels—the left anterior descending, the left circumflex, and the right coronary arteries with the left anterior descending and left circumflex arteries arising from the left main coronary artery (**Fig. 13-4**). When the right coronary artery is the origin of the atrioventricular nodal branch, the posterior descending artery, and the posterior lateral vessels, the circulation is defined as right dominant; this is found in ~85% of individuals. When these branches arise from the left circumflex artery as occurs in ~5% of individuals, the circulation is defined as left dominant. The remaining ~10% of patients have a codominant circulation with vessels arising from both the right and left coronary circulation. In some patients, a ramus intermedius branch arises directly from the left main coronary artery; this finding is a normal variant. Coronary artery anomalies occur in 1–2% of patients, with separate ostia for the left anterior descending and left circumflex arteries being the most common (0.41%).

Coronary angiography visualizes coronary artery stenoses as luminal narrowings on the cine angiogram. The degree of narrowing is referred to as the percent stenosis and is determined visually by comparing the most severely diseased segment with a proximal or distal “normal segment”; a stenosis >50% is considered significant (**Fig. 13-5**). Online quantitative coronary angiography can provide a more accurate assessment of the percent stenosis and lessen the tendency to overestimate lesion severity visually. The presence of a myocardial bridge, which most commonly involves the left anterior descending artery, may be mistaken for a significant stenosis; this occurs when a portion of the vessel dips below the epicardial surface into the myocardium and is subject to compressive forces during ventricular systole. The key to differentiating a myocardial bridge from a fixed stenosis is that the “stenosed”

part of the vessel returns to normal during diastole. Coronary calcification is also seen during angiography prior to the injection of contrast agents. Collateral blood vessels may be seen traversing from one vessel to the distal vasculature of a severely stenosed or totally

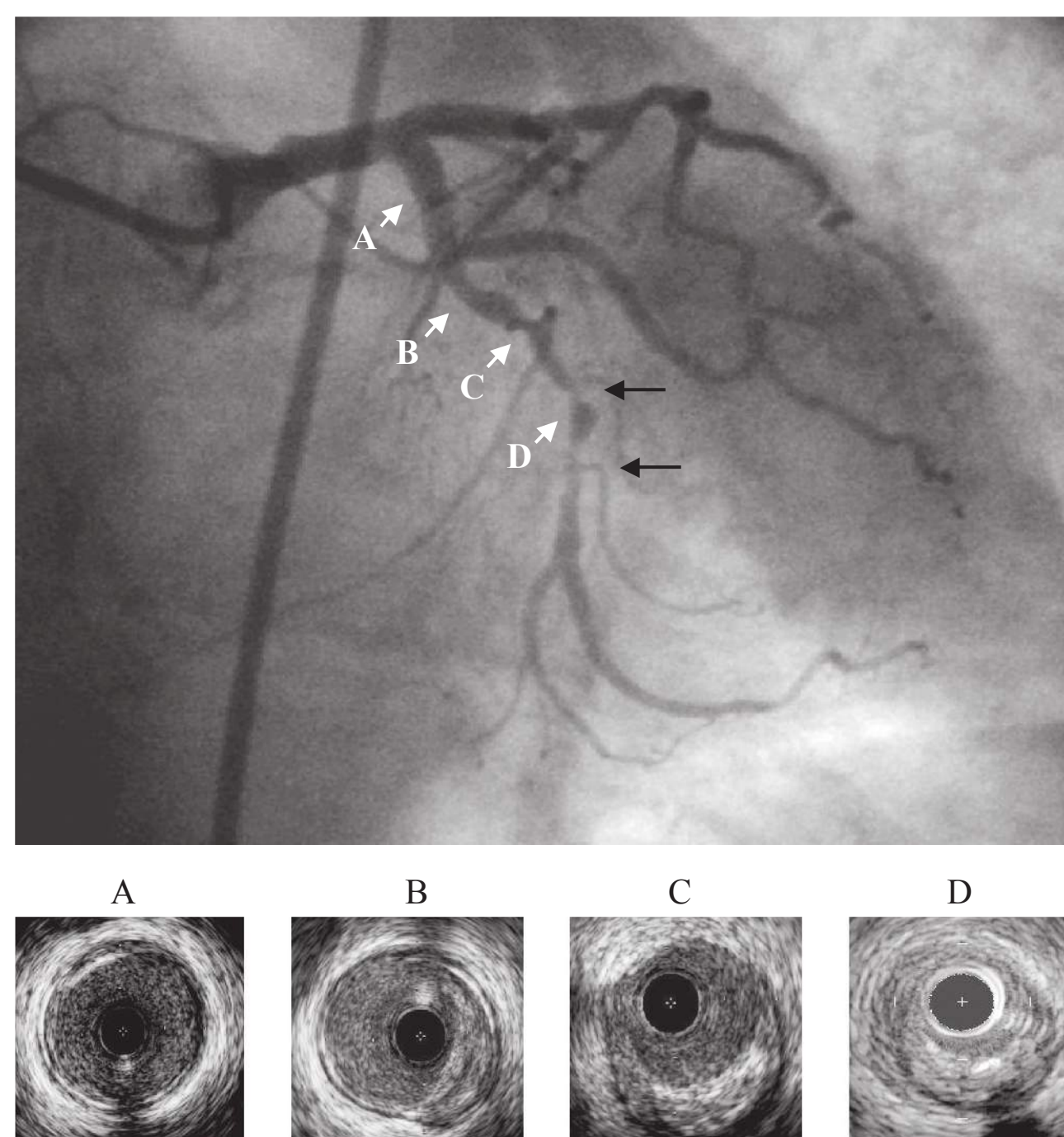


FIGURE 13-5

Coronary stenoses on cine angiogram and intravascular ultrasound. Significant stenoses in the coronary artery are seen as narrowings (black arrows) of the vessel. Intravascular ultrasound shows a normal segment of artery (A), areas with eccentric plaque (B, C), and near total obliteration of the lumen at the site of the significant stenosis (D). Note that the intravascular ultrasound catheter is present in the images as a black circle.

occluded vessel. Thrombolysis in myocardial infarction (TIMI) flow grade, a measure of the relative duration of time that it takes for contrast to opacify the coronary artery fully, may provide an additional clue to the degree of lesion severity, and the presence of TIMI grade 1 (minimal filling) or 2 (delayed filling) suggests that a significant coronary artery stenosis is present.

INTRAVASCULAR ULTRASOUND, OPTICAL COHERENCE TOMOGRAPHY, AND FRACTIONAL FLOW RESERVE

During coronary angiography, intermediate stenoses (40–70%), indeterminate findings, or anatomic findings that are incongruous with the patient's symptoms may require further interrogation. In these cases, intravascular ultrasound provides a more accurate anatomic assessment of the coronary artery and the degree of coronary atherosclerosis (Fig. 13-5). Intravascular ultrasound (IVUS) is performed using a small flexible catheter with a 40-MHz transducer at its tip that is advanced into the coronary artery over a guidewire. Data from intravascular ultrasound studies may be used to image atherosclerotic plaque precisely, determine luminal cross-sectional area, and measure vessel size; it is also used during or following percutaneous coronary intervention to assess the stenosis and determine the adequacy of stent placement. Optical coherence tomography (OCT) is a catheter-based imaging technique that uses near-infrared light to generate images with better spatial resolution than IVUS; however, the depth of field is smaller. The advantage of OCT imaging over IVUS lies in its ability to image characteristics of the atherosclerotic plaque (lipid, fibrous cap) with high definition and to assess coronary stent placement, apposition, and patency (Fig. 13-6).

Measurement of the fractional flow reserve provides a functional assessment of the stenosis and is more accurate in predicting long-term clinical outcome than imaging techniques. The fractional flow reserve is the

ratio of the pressure in the coronary artery distal to the stenosis divided by the pressure in the artery proximal to the stenosis at maximal vasodilation. Fractional flow reserve is measured using a coronary pressure-sensor guidewire at rest and at maximal hyperemia following the injection of adenosine. A fractional flow reserve of <0.80 indicates a hemodynamically significant stenosis that would benefit from intervention.

POSTPROCEDURE CARE

Once the procedure is completed, vascular access sheaths are removed. If the femoral approach is used, direct manual compression or vascular closure devices that immediately close the arteriotomy site with a staple/clip, collagen plug, or sutures are used to achieve hemostasis. These devices decrease the length of supine bed rest (from 6 hours to 2–4 hours) and improve patient satisfaction but have not been shown definitively to be superior to manual compression with respect to access-site complications. With radial-artery access, bed rest is needed for only 2 hours. When cardiac catheterization is performed as an elective outpatient procedure, the patient completes postprocedure bed rest in a monitored setting and is discharged home with instructions to liberalize fluids because contrast agents promote an osmotic diuresis, to avoid strenuous activity, and to observe the vascular access site for signs of complications. Overnight hospitalization may be required for high-risk patients with significant comorbidities, patients with complications occurring during the catheterization, or patients who have undergone a percutaneous coronary intervention. Hypotension early after the procedure may be due to inadequate fluid replacement or retroperitoneal bleeding from the access site. Patients who received >2 Gy of radiation during the procedure should be examined for signs of erythema. For patients who received higher doses (>5 Gy), clinical follow-up within 1 month to assess for skin injury is recommended.

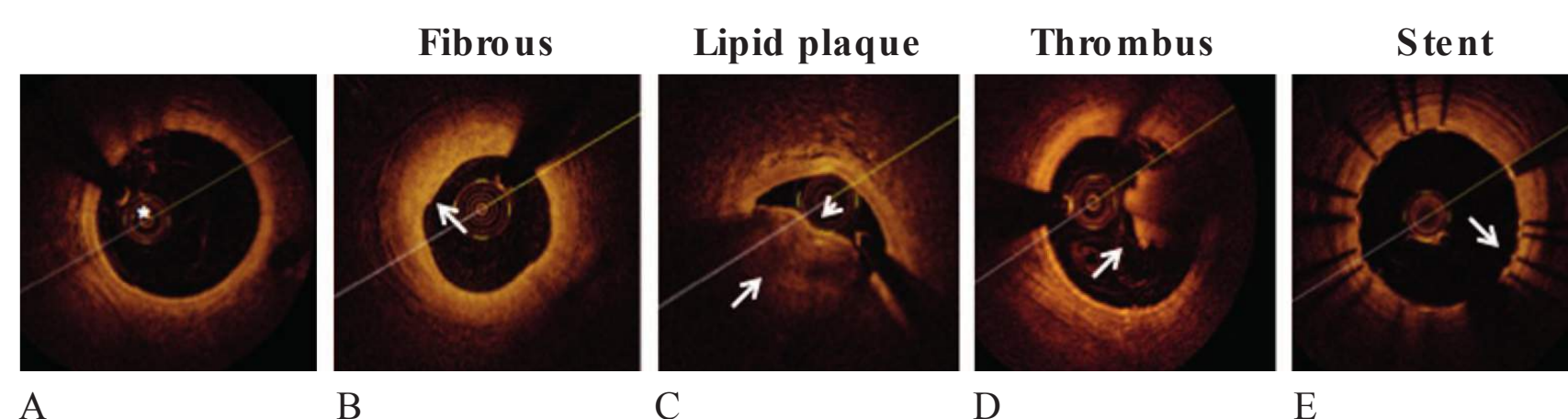


FIGURE 13-6

Optical coherence tomography imaging. A. The optical coherence tomography (OCT) catheter (*) in the lumen of a coronary artery with limited neointima formation. The intima is seen with high definition, but unlike intravascular ultrasound imaging, the vessel media and adventitia are not well visualized. B. A fibrous plaque (arrow) is characterized by a bright signal. C. A large, eccentric, lipid-rich plaque obscures part of the vessel

lumen. Because lipid in the plaque absorbs light, the lipid-rich plaque appears as a dark area with irregular borders (arrow). The plaque is covered by a thin fibrous cap (arrowhead) typical of a vulnerable plaque. D. A thrombus (arrow) adherent to a ruptured plaque that is protruding into the vessel lumen. E. A coronary stent is that is well opposed to the vessel wall. The stent struts appear as short bright lines with dropout behind the struts (arrow).

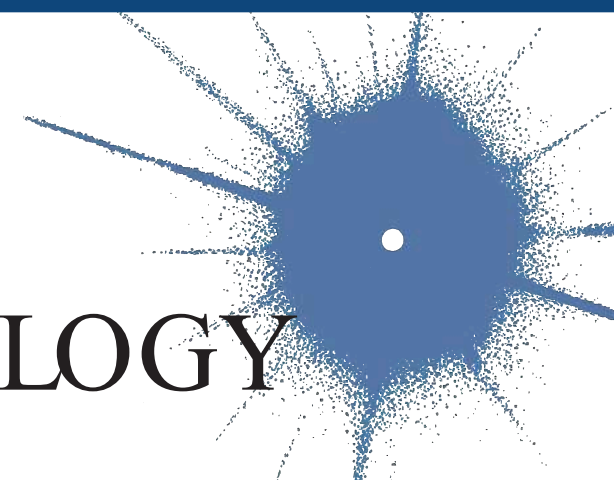
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SECTION III

HEART RHYTHM DISTURBANCES

CHAPTER 14

PRINCIPLES OF ELECTROPHYSIOLOGY



David D. Spragg ■ Gordon F. Tomaselli

HISTORY AND INTRODUCTION

The field of cardiac electrophysiology was ushered in with the development of the electrocardiogram (ECG) by Einthoven at the turn of the twentieth century. Subsequent recording of cellular membrane currents demonstrated that the body surface ECG is the timed sum of the cellular action potentials in the atria and ventricles. In the late 1960s, the development of intracavitary recording, in particular, His bundle electrograms, marked the beginning of contemporary clinical electrophysiology. Adoption of radiofrequency technology to ablate cardiac tissue in the early 1990s heralded the birth of interventional cardiac electrophysiology.

The clinical problem of sudden death caused by ventricular arrhythmias, most commonly in the setting of coronary artery obstruction, was recognized as early as the late nineteenth century. The problem was vexing and led to the development of pharmacologic and nonpharmacologic therapies, including transthoracic defibrillators, cardiac massage, and, most recently, implantable defibrillators. Over time the limitations of antiarrhythmic drug therapy have been highlighted repeatedly in clinical trials, and now ablation and devices are first-line therapy for a number of cardiac arrhythmias.

In the last two decades, the genetic basis of a number of heritable arrhythmias has been elucidated, revealing important insights into the mechanisms not only of these rare arrhythmias but also of similar rhythm disturbances observed in more common forms of heart disease.

DESCRIPTIVE PHYSIOLOGY

The normal cardiac impulse is generated by pacemaker cells in the sinoatrial node situated at the junction of the right atrium and the superior vena cava (see Fig. 11-1). This impulse is transmitted slowly through nodal tissue

to the anatomically complex atria, where it is conducted more rapidly to the atrioventricular node (AVN), inscribing the P wave of the ECG (see Fig. 11-2). There is a perceptible delay in conduction through the anatomically and functionally heterogeneous AVN. The time needed for activation of the atria and the AVN delay is represented as the PR interval of the ECG. The AVN is the only electrical connection between the atria and the ventricles in the normal heart. The electrical impulse emerges from the AVN and is transmitted to the His-Purkinje system, specifically the common bundle of His, then the left and right bundle branches, and then to the Purkinje network, facilitating activation of ventricular muscle. In normal circumstances, the ventricles are activated rapidly in a well-defined fashion that is determined by the course of the Purkinje network, and this inscribes the QRS complex (see Fig. 11-2). Recovery of electrical excitability occurs more slowly and is governed by the time of activation and duration of regional action potentials. The relative brevity of epicardial action potentials in the ventricle results in repolarization that occurs first on the epicardial surface and then proceeds to the endocardium, which inscribes a T wave normally of the same polarity as the QRS complex. The duration of ventricular activation and recovery is determined by the action potential duration and is represented on the body surface ECG by the QT interval (see Fig. 11-2).

Cardiac myocytes exhibit a characteristically long action potential (200–400 ms) compared with neurons and skeletal muscle cells (1–5 ms). The action potential profile is sculpted by the orchestrated activity of multiple distinctive time- and voltage-dependent ionic currents (Fig. 14-1A). The currents are carried by transmembrane proteins that passively conduct ions down their electrochemical gradients through selective pores (ion channels), actively transport ions against their electrochemical gradient (pumps, transporters), or electrogenically exchange ionic species (exchangers).

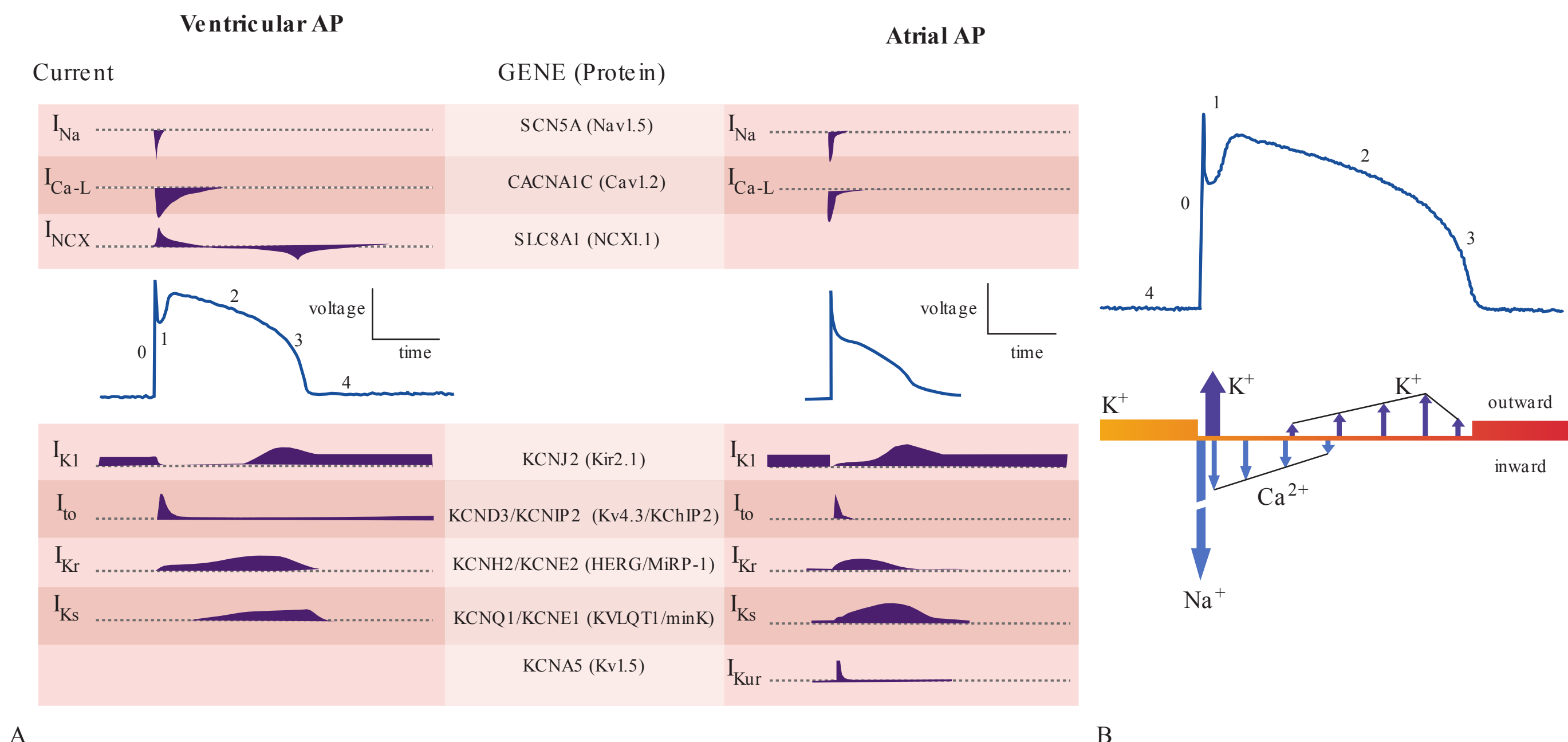


FIGURE 14-1

A. Cellular atrial and ventricular action potentials. Phases 0–4 are the rapid upstroke, early repolarization, plateau, late repolarization, and diastole, respectively. The ionic currents and their respective genes are shown above and below the action potentials. The currents that underlie the action potentials vary in atrial and ventricular myocytes. B. A ventricular action potential with a schematic of the ionic currents flowing during the phases of the action potential. Potassium current (I_{Kl}) is the principal current

during phase 4 and determines the resting membrane potential of the myocyte. Sodium current generates the upstroke of the action potential (phase 0); activation of I_{to} with inactivation of the Na current inscribes early repolarization (phase 1). The plateau (phase 2) is generated by a balance of repolarizing potassium currents and depolarizing calcium current. Inactivation of the calcium current with persistent activation of potassium currents (predominantly I_{Kr} and I_{Ks}) causes phase 3 repolarization.

Action potentials in the heart are regionally distinct. The regional variability in cardiac action potentials is a result of differences in the number and types of ion channel proteins expressed by different cell types in the heart. Further, unique sets of ionic currents are active in pacemaking and muscle cells, and the relative contributions of these currents may vary in the same cell type in different regions of the heart (Fig. 14-1A).

Ion channels are complex, multisubunit transmembrane glycoproteins that open and close in response to a number of biologic stimuli, including a change in membrane voltage, ligand binding (directly to the channel or to a G protein–coupled receptor), and mechanical deformation (Fig. 14-2). Other ion motive exchangers and transporters contribute importantly to cellular excitability in the heart. Ion pumps establish and maintain the ionic gradients across the cell membrane that serve as the driving force for current flow through ion channels. Transporters or exchangers that do not move ions in an electrically neutral manner (e.g., the sodium–calcium exchanger transports three Na^+ for one Ca^{2+}) are termed electrogenic and contribute directly to the action potential profile.

The most abundant superfamily of ion channels expressed in the heart is voltage gated. Several structural themes are common to all voltage-dependent ion channels. First, the architecture is modular, consisting either of four homologous subunits (e.g., K channels) or of four internally homologous domains (e.g., Na and Ca channels). Second, the proteins fold around a central pore lined by amino acids that exhibit exquisite conservation within a given channel family of like selectivity (e.g., all Na channels have very similar P segments). Third, the general strategy for activation gating (opening and closing in response to changes in membrane voltage) is highly conserved: the fourth transmembrane segment (S4), studded with positively charged residues, lies within the membrane field and moves in response to depolarization, opening the channel. Fourth, most ion channel complexes include not only the pore-forming proteins (α subunits) but also auxiliary subunits (e.g., β subunits) that modify channel function (Fig. 14-2).

Na and Ca channels are the primary carriers of depolarizing current in both the atria and the ventricles; inactivation of these currents and activation of repolarizing K currents hyperpolarize the heart cells,

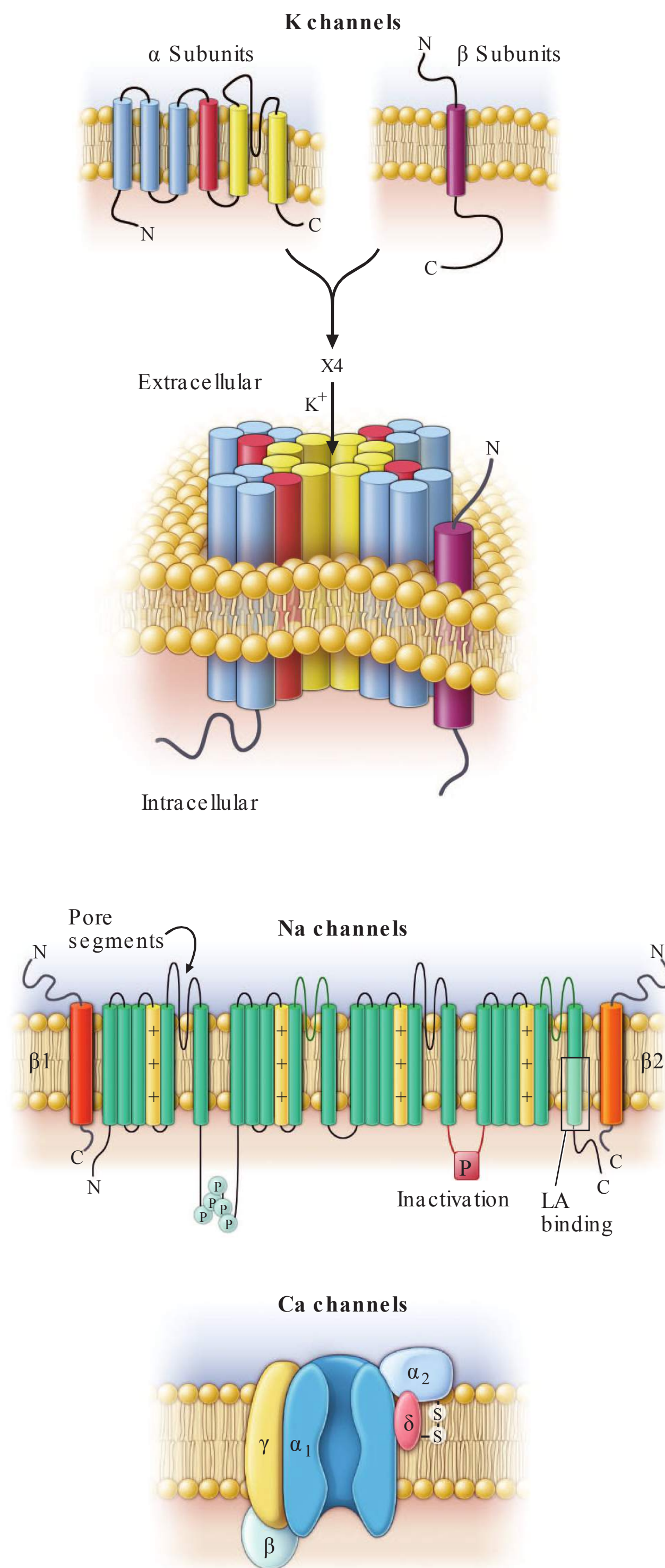


FIGURE 14-2

Topology and subunit composition of the voltage-dependent ion channels. Potassium channels are formed by the tetramerization of α or pore-forming subunits and one or more β subunits; only single β subunits are shown for clarity. Sodium and calcium channels are composed of α subunits with four homologous domains and one or more ancillary subunits. In all channel types, the loop of protein between the fifth and sixth membrane-spanning repeat in each subunit or domain forms the

ion-selective pore. In the case of the sodium channel, the channel is a target for phosphorylation, the linker between the third and fourth homologous domain is critical to inactivation, and the sixth membrane-spanning repeat in the fourth domain is important in local anesthetic antiarrhythmic drug binding. The Ca channel is a multisubunit protein complex with the α_1 subunit containing the pore and major drug binding domain.

reestablishing the negative resting membrane potential (Fig. 14-1B). The plateau phase is a time when little current is flowing, and relatively minor changes in depolarizing or repolarizing currents can have profound effects on the shape and duration of the action profile. Mutations in subunits of these channel proteins produce arrhythmogenic alterations in the action potentials that cause long and short QT syndrome, Brugada syndrome, idiopathic ventricular fibrillation, familial atrial fibrillation, and some forms of conduction system disease.

MECHANISMS OF CARDIAC ARRHYTHMIAS

Cardiac arrhythmias result from abnormalities of electrical impulse generation, conduction, or both. Bradyarrhythmias typically arise from disturbances in impulse formation at the level of the sinoatrial node or from disturbances in impulse propagation at any level, including exit block from the sinus node, conduction block in the AVN, and impaired conduction in the His-Purkinje system. Tachyarrhythmias can be classified according to mechanism, including enhanced automaticity (spontaneous depolarization of atrial, junctional, or ventricular pacemakers), triggered arrhythmias (initiated by afterdepolarizations occurring during or immediately after cardiac repolarization, during phase 3 or 4 of the action potential), or reentry (circus propagation

of a depolarizing wavefront). A variety of mapping and pacing maneuvers typically performed during invasive electrophysiologic testing can often determine the underlying mechanism of a tachyarrhythmia (Table 14-1).

Alterations in impulse initiation: automaticity

Spontaneous (phase 4) diastolic depolarization underlies the property of automaticity characteristic of pacemaking cells in the sinoatrial (SA) and atrioventricular (AV) nodes, His-Purkinje system, coronary sinus, and pulmonary veins. Phase 4 depolarization results from the concerted action of a number of ionic currents, including K⁺ currents, Ca²⁺ currents, electrogenic Na, K-ATPase, the Na-Ca exchanger, and the so-called funny, or pacemaker, current (I_f); however, the relative importance of these currents remains controversial.

The rate of phase 4 depolarization and, therefore, the firing rates of pacemaker cells are dynamically regulated. Prominent among the factors that modulate phase 4 is autonomic nervous system tone. The negative chronotropic effect of activation of the parasympathetic nervous system is a result of the release of acetylcholine that binds to muscarinic receptors, releasing G protein βγ subunits that activate a potassium current (I_{KACH}) in nodal and atrial cells. The resulting increase in K⁺ conductance opposes membrane depolarization, slowing the rate of

TABLE 14-1

ARRHYTHMIA MECHANISMS			
ELECTROPHYSIOLOGIC PROPERTY	MOLECULAR COMPONENTS	MECHANISM	PROTOTYPIC ARRHYTHMIAS
Cellular			
Impulse Initiation			
Automaticity	I _f , I _{Ca-L} , I _{Ca-T} , I _K , I _{Kl}	Suppression/acceleration of phase 4	Sinus bradycardia, sinus tachycardia
Triggered automaticity	Calcium overload, I _{TL}	DADs	Digitalis toxicity, reperfusion VT
	I _{Ca-L} , I _K , I _{Na}	EADs	Torsades des pointes, congenital and acquired
Excitation	I _{Na}	Suppression of phase 0	Ischemic VF
	I _{K-ATP}	AP shortening, inexcitability	
	I _{Ca-L}	Suppression	AVblock
Repolarization	I _{Na} , I _{Ca-L} , I _K , I _{Kl} , Ca ²⁺ homeostasis	AP prolongation, EADs, DADs	Polymorphic VT (HF, LVH)
	I _{Ca-L} , Kchannels, Ca ²⁺ homeostasis	AP shortening	Atrial fibrillation
Multicellular			
Cellular Coupling	Connexins (Cx43), I _{Na} , I _{K-ATP}	Decreased coupling	Ischemic VT/VF
Tissue Structure	Extracellular matrix, collagen	Excitable gap and functional reentry	Monomorphic VT, atrial fibrillation

Abbreviations: AP, action potential; AV, atrioventricular; DADs, delayed afterdepolarizations; EADs, early afterdepolarizations; HF, heart failure; LVH, left ventricular hypertrophy; VF, ventricular fibrillation; VT, ventricular tachyarrhythmia.

rise of phase 4 of the action potential. Conversely, augmentation of sympathetic nervous system tone increases myocardial catecholamine concentrations, which activate both α - and β -adrenergic receptors. The effect of β_1 -adrenergic stimulation predominates in pacemaking cells, augmenting both L-type Ca current (I_{Ca-L}) and I_f , thus increasing the slope of phase 4. Enhanced sympathetic nervous system activity can dramatically increase the rate of firing of SA nodal cells, producing sinus tachycardia with rates >200 beats/min. By contrast, the increased rate of firing of Purkinje cells is more limited, rarely producing ventricular tachyarrhythmias >120 beats/min.

Normal automaticity may be affected by a number of other factors associated with heart disease. Hypokalemia and ischemia may reduce the activity of Na, K-ATPase, thereby reducing the background repolarizing current and enhancing phase 4 diastolic depolarization. The end result would be an increase in the spontaneous firing rate of pacemaking cells. Modest increases in extracellular potassium may render the maximum diastolic potential more positive, thereby also increasing the firing rate of pacemaking cells. A more significant increase in $[K^+]_o$, however, renders the heart inexcitable by depolarizing the membrane potential.

Normal or enhanced automaticity of subsidiary latent pacemakers produces escape rhythms in the setting of failure of more dominant pacemakers. Suppression of a pacemaker cell by a faster rhythm leads to an increased intracellular Na^+ load ($[Na^+]_i$), and extrusion of Na^+ from the cell by Na, K-ATPase produces an increased background repolarizing current that slows phase 4 diastolic depolarization. At slower rates, $[Na^+]_i$ is decreased, as is the activity of the Na, K-ATPase, resulting in progressively more rapid diastolic depolarization and warm-up of the tachycardia rate. Overdrive suppression and warm-up are characteristic of, but may not be observed in, all automatic tachycardias. Abnormal conduction into tissue with enhanced automaticity (entrance block) may blunt or eliminate the phenomena of overdrive suppression and warm-up of automatic tissue.

Abnormal automaticity may produce atrial tachycardia, accelerated idioventricular rhythms, and ventricular tachycardia, particularly associated with ischemia and reperfusion. It has also been suggested that injury currents at the borders of ischemic myocardium may depolarize adjacent nonischemic tissue, predisposing to automatic ventricular tachycardia.

Afterdepolarizations and triggered automaticity

Triggered automaticity or activity refers to impulse initiation that is dependent on afterdepolarizations (Fig. 14-3). Afterdepolarizations are membrane voltage oscillations that occur during (early afterdepolarizations,

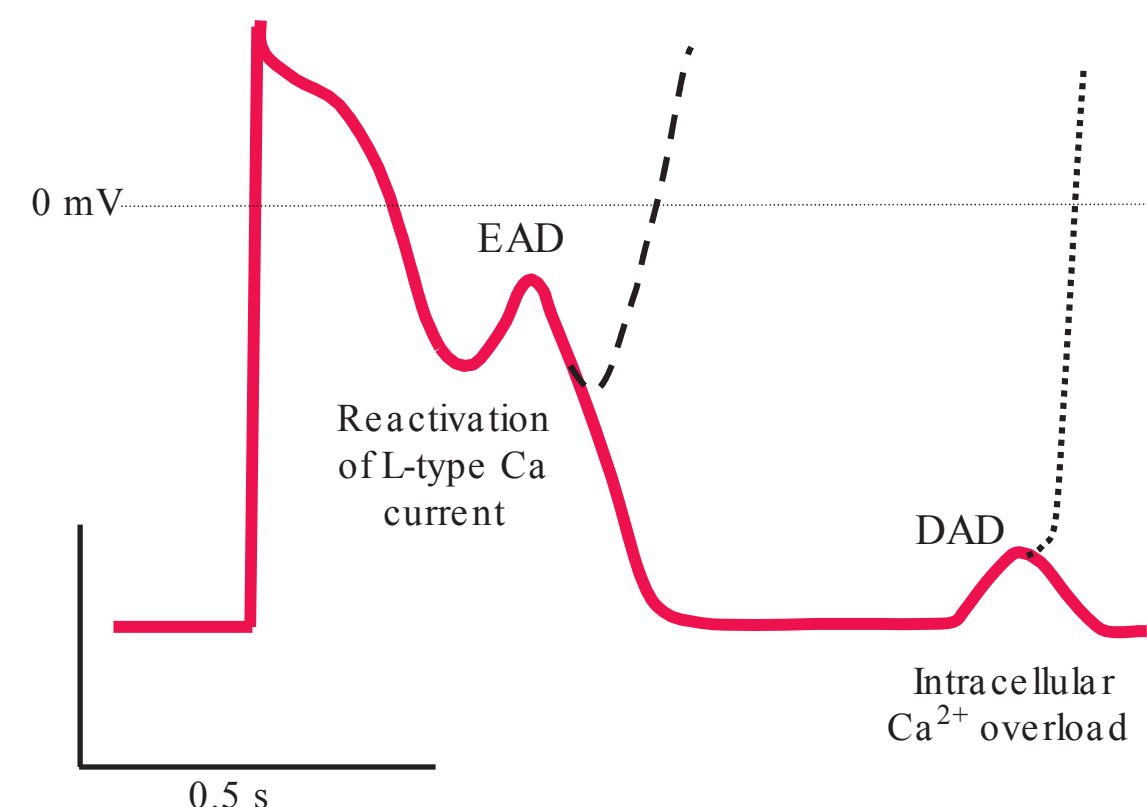


FIGURE 14-3

Schematic action potentials with early after-depolarizations (EADs) and delayed afterdepolarizations (DADs). Afterdepolarizations are spontaneous depolarizations in cardiac myocytes. EADs occur before the end of the action potential (phases 2 and 3), interrupting repolarization. DADs occur during phase 4 of the action potential after completion of repolarization. The cellular mechanisms of EADs and DADs differ (see text).

EADs) or after (delayed afterdepolarizations, DADs) an action potential.

The cellular feature common to the induction of DADs is the presence of an increased Ca^{2+} load in the cytosol and sarcoplasmic reticulum. Digitalis glycoside toxicity, catecholamines, and ischemia all can enhance Ca^{2+} loading sufficiently to produce DADs. Accumulation of lysophospholipids in ischemic myocardium with consequent Na^+ and Ca^{2+} overload has been suggested as a mechanism for DADs and triggered automaticity. Cells from damaged areas or cells that survive a myocardial infarction may display spontaneous release of calcium from the sarcoplasmic reticulum, and this may generate “waves” of intracellular calcium elevation and arrhythmias.

EADs occur during the action potential and interrupt the orderly repolarization of the myocyte. Traditionally, EADs have been thought to arise from action potential prolongation and reactivation of depolarizing currents, but more recent experimental evidence suggests a previously unappreciated interrelationship between intracellular calcium loading and EADs. Cytosolic calcium may increase when action potentials are prolonged. This, in turn, appears to enhance L-type Ca current, further prolonging action potential duration as well as providing the inward current driving EADs. Intracellular calcium loading by action potential prolongation may also enhance the likelihood of DADs. The interrelationship among intracellular $[Ca^{2+}]$, EADs, and DADs may be one explanation for the susceptibility of hearts that are calcium loaded (e.g., in ischemia or congestive heart failure) to develop arrhythmias, particularly on exposure to action potential-prolonging drugs.

EAD-triggered arrhythmias exhibit rate dependence. In general, the amplitude of an EAD is augmented at

slow rates when action potentials are longer. Indeed, a fundamental condition that underlies the development of EADs is action potential and QT prolongation. Hypokalemia, hypomagnesemia, bradycardia, and, most commonly, drugs can predispose to the generation of EADs, invariably in the context of prolonging the action potential. Antiarrhythmics with class IA and III action (see below) produce action potential and QT prolongation intended to be therapeutic but frequently causing arrhythmias. Noncardiac drugs such as phenothiazines, nonsedating antihistamines, and some antibiotics can also prolong the action potential duration and predispose to EAD-mediated triggered arrhythmias. Decreased $[K^+]_o$ paradoxically may decrease membrane potassium currents (particularly the delayed rectifier current, I_{Kr}) in the ventricular myocyte, explaining why hypokalemia causes action potential prolongation and EADs. In fact, potassium infusions in patients with the congenital long QT syndrome (LQTS) and in those with drug-induced acquired QT prolongation shorten the QT interval.

EAD-mediated triggered activity probably underlies initiation of the characteristic polymorphic ventricular tachycardia, torsades des pointes, seen in patients with congenital and acquired forms of LQTS. Structural heart disease, such as cardiac hypertrophy and heart failure, may also delay ventricular repolarization (so-called electrical remodeling) and predispose to arrhythmias related to abnormalities of repolarization. The abnormalities of repolarization in hypertrophy and heart failure are often magnified by concomitant drug therapy or electrolyte disturbances.

Abnormal impulse conduction: reentry

The most common arrhythmia mechanism is reentry resulting from abnormal electrical impulse conduction and is defined as the circulation of an activation wave around an inexcitable obstacle. The requirements for reentry are two electrophysiologically dissimilar pathways for impulse propagation around an inexcitable region (Fig. 14-4). Reentry can occur around a fixed anatomic structure (e.g., myocardial scar), with a stable pattern of cardiac depolarization moving in series over the anterograde and retrograde limbs of the circuit. This form of reentry, referred to as anatomic reentry or excitable gap reentry (see below), is initiated when a depolarizing wavefront encounters an area of unidirectional conduction block in the retrograde limb of the circuit. Conduction across the anterograde limb occurs with a delay that, if of sufficient duration, allows for recovery of conduction in the retrograde limb with reentry of the depolarization wave into the retrograde limb of the circuit. Sustained reentry requires that the functional dimension of depolarized tissue or the tachycardia wavelength ($\lambda = \text{conduction velocity} \times \text{refractory}$

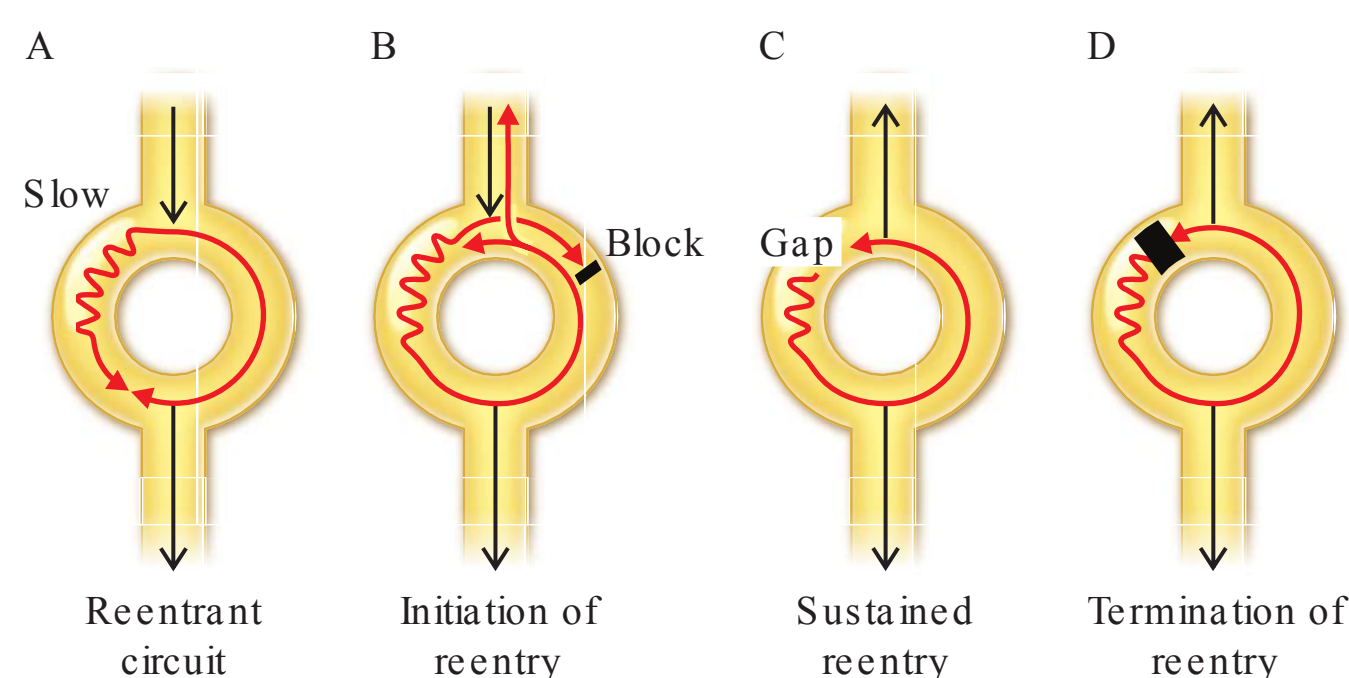


FIGURE 14-4

Schematic diagram of reentry. A. The circuit contains two limbs, one with slow conduction. B. A premature impulse blocks in the fast pathway and conducts over the slow pathway, allowing the fast pathway to recover so that the activation wave can reenter the fast pathway from the retrograde direction. C. During sustained reentry utilizing such a circuit, a gap (excitable gap) exists between the activating head of the wave and the recovering tail. D. One mechanism of termination of reentry occurs when the conduction and recovery characteristics of the circuit change and the activating head of the wave collides with the tail, extinguishing the tachycardia.

period) fits within the total anatomic length of the circuit, referred to as the path length. When the path length of the circuit exceeds the λ of the tachycardia, the region between the head of the activation wave and the refractory tail is referred to as the excitable gap. Anatomically determined, excitable gap reentry can explain several clinically important tachycardias, such as AV reentry, atrial flutter, bundle branch reentry ventricular tachycardia, and ventricular tachycardia in scarred myocardium.

Reentrant arrhythmias may exist in the heart in the absence of an excitable gap and with a tachycardia wavelength nearly the same size as the path length. In this case, the wavefront propagates through partially refractory tissue without a fixed anatomic obstacle and no fully excitable gap; this is referred to as leading circle reentry, a form of functional reentry (reentry that depends on functional properties of the tissue). Unlike excitable gap reentry, there is no fixed anatomic circuit in leading circle reentry, and it may, therefore, not be possible to disrupt the tachycardia with pacing or destruction of a part of the circuit. Furthermore, the circuit in leading circle reentry tends to be less stable than that in excitable gap reentrant arrhythmias, with large variations in cycle length and a predilection to termination. There is strong evidence to suggest that less organized arrhythmias, such as atrial and ventricular fibrillation, are associated with more complex activation of the heart and are due to functional reentry.

Catheter-based and pharmacologic therapies for reentrant arrhythmias are designed to disrupt the anatomic

circuit or alter the relationship between the wavelength and path length of the arrhythmia circuit, eliminating pathologic conduction. For example, antiarrhythmic drugs that prolong the action potential (Class III) are effective if they sufficiently prolong the λ such that it can no longer fit within the anatomic circuit. Catheter ablation is often undertaken with the goal of identifying and destroying a critical limb of the reentrant circuit (i.e., ablation of the cavotricuspid isthmus in the treatment of typical, right atrial flutter). Due to the less defined pathways of myocardial activation seen in functional reentry, ablation of these rhythms tends to target initiating triggers (e.g., pulmonary vein potentials in catheter ablation of atrial fibrillation) rather than the anatomic circuit.

Structural heart disease is associated with changes in conduction and refractoriness that increase the risk of reentrant arrhythmias. Chronically ischemic myocardium exhibits a downregulation of the gap junction channel protein (connexin 43) that carries intercellular ionic current. The border zones of infarcted and failing ventricular myocardium exhibit not only functional alterations of ionic currents but also remodeling of tissue and altered distribution of gap junctions. The changes in gap junction channel expression and distribution, in combination with macroscopic tissue alterations, support a role for slowed conduction in reentrant arrhythmias that complicate chronic coronary artery disease (CAD). Aged human atrial myocardium exhibits altered conduction, manifest as highly fractionated atrial electrograms, producing an ideal substrate for the reentry that may underlie the very common development of atrial fibrillation in the elderly.

APPROACH TO THE PATIENT

Cardiac Arrhythmias

The evaluation of patients with suspected cardiac arrhythmias is highly individualized; however, two key features—the history and ECG—are pivotal in directing the diagnostic workup and therapy. Patients with cardiac arrhythmias exhibit a wide spectrum of clinical presentations that range from asymptomatic ECG abnormalities to survival from cardiac arrest. In general, the more severe the presenting symptoms are, the more aggressive the evaluation and treatment are. Loss of consciousness that is believed to be of cardiac origin typically mandates an exhaustive search for the etiology and often requires invasive, device-based therapy. The presence of structural heart disease and prior myocardial infarction dictates a change in the approach to the management of syncope or ventricular arrhythmias. The presence of a family history of serious ventricular arrhythmias or premature sudden

death will influence the evaluation of presumed heritable arrhythmias.

The physical examination is focused on determining whether there is cardiopulmonary disease that is associated with specific cardiac arrhythmias. The absence of significant cardiopulmonary disease often, but not always, suggests benignity of the rhythm disturbance. In contrast, palpitations, syncope, or near syncope in the setting of significant heart or lung disease have more ominous implications. In addition, the physical examination may reveal the presence of a persistent arrhythmia such as atrial fibrillation.

The judicious use of noninvasive diagnostic tests is an important element in the evaluation of patients with arrhythmias, and there is no test more important than the ECG, particularly if recorded at the time of symptoms. Uncommon but diagnostically important signatures of electrophysiologic disturbances may be unearthed on the resting ECG, such as delta waves in Wolff-Parkinson-White (WPW) syndrome, prolongation or shortening of the QT interval, right precordial ST-segment abnormalities in Brugada syndrome, and epsilon waves in arrhythmogenic right ventricular dysplasia. Variants of body surface ECG recording can provide important information about arrhythmia substrates and triggers. Holter monitoring and event recording, either continuous or intermittent, record the body surface ECG over longer periods, enhancing the possibility of observing the cardiac rhythm during symptoms. Holter monitoring is particularly useful in assessing daily symptoms thought to be attributable to arrhythmia or for quantifying a particular arrhythmia phenomenon (e.g., premature ventricular complex burden). Ambulatory event monitors are indicated when symptoms thought to be due to arrhythmia occur less frequently (i.e., several episodes per month), and, because the monitors are typically patient-activated, they are optimal for correlating symptoms with rhythm disturbances. Implantable long-term monitors permit prolonged telemetric monitoring both for diagnosis and to assess the efficacy of therapy. Implantable monitors are typically used for the evaluation of malignant symptoms that occur quite infrequently and that cannot be provoked at diagnostic electrophysiology study.

Exercise electrocardiography is important in determining the presence of myocardial demand ischemia; more recently, analysis of the morphology of the QT interval with exercise has been used to assess the risk of serious ventricular arrhythmias. The exercise ECG may be particularly useful in patients with symptoms that occur during activity. Cardiac imaging plays an important role in the detection and characterization of myocardial structural abnormalities that may render the heart more susceptible to arrhythmia. Ventricular tachyarrhythmias, for instance, occur more frequently in patients with ventricular systolic dysfunction and chamber dilation, in hypertrophic

cardiomyopathy, and in the setting of infiltrative diseases such as sarcoidosis. Supraventricular arrhythmias may be associated with particular congenital conditions, including AV reentry in the setting of Ebstein's anomaly. Echocardiography is a frequently employed imaging technique to screen for disorders of cardiac structure and function. Increasingly, magnetic resonance imaging of the myocardium is being used to screen for scar burden, fibrofatty infiltration of the myocardium as seen in arrhythmogenic right ventricular cardiomyopathy, and other structural changes that affect arrhythmia susceptibility.

Head-up tilt (HUT) testing is useful in the evaluation of patients with syncope in whom there is a suspicion that exaggerated vagal tone or vasodepression may play a causal role. The physiologic response to HUT is incompletely understood; however, redistribution of blood volume and increased ventricular contractility occur consistently. Exaggerated activation of a central reflex in response to HUT produces a stereotypic response of an initial increase in heart rate, then a drop in blood pressure followed by a reduction in heart rate characteristic of neurally mediated hypotension. Other responses to HUT may be observed in patients with orthostatic hypotension and autonomic insufficiency. HUT is used most often in patients with recurrent syncope, although it may be useful in patients with single syncopal episodes with associated injury, particularly in the absence of structural heart disease. In patients with structural heart disease, HUT may be indicated in those with syncope, in whom other causes (e.g., asystole, ventricular tachyarrhythmias) have been excluded. HUT has been suggested as a useful tool in the diagnosis of and therapy for recurrent idiopathic vertigo, chronic fatigue syndrome, recurrent transient ischemic attacks, and repeated falls of unknown etiology in the elderly. Importantly, HUT is relatively contraindicated in the presence of severe CAD with proximal coronary stenoses, known severe cerebrovascular disease, severe mitral stenosis, and obstruction to left ventricular outflow (e.g., aortic stenosis).

Electrophysiologic testing is central to the understanding and treatment of many cardiac arrhythmias. Indeed, most frequently, electrophysiologic testing is interventional, providing both diagnosis and therapy. The indications for electrophysiologic testing fall into several categories: to define the mechanism of an arrhythmia; to deliver catheter-based ablative treatment; and to determine the etiology of symptoms that may be caused by an arrhythmia (e.g., syncope, palpitations). The components of the electrophysiologic test are baseline measurements of conduction under resting and stressed (rate or pharmacologic) conditions and maneuvers, both pacing and pharmacologic, to induce arrhythmias. A number of sophisticated electrical mapping and catheter-guidance techniques have been developed to facilitate catheter-based therapeutics in the electrophysiology laboratory.

TREATMENT Cardiac Arrhythmias

ANTIARRHYTHMIC DRUG THERAPY The interaction of antiarrhythmic drugs with cardiac tissues and the resulting electrophysiologic changes are complex. An incomplete understanding of the effects of these drugs has produced serious missteps that have had adverse effects on patient outcomes and the development of newer pharmacologic agents. Currently, antiarrhythmic drugs have been relegated to an ancillary role in the treatment of most cardiac arrhythmias.

There are several explanations for the complexity of antiarrhythmic drug action: the structural similarity of target ion channels; regional differences in the levels of expression of channels and transporters, which change with disease; time and voltage dependence of drug action; and the effect of these drugs on targets other than ion channels. Because of the limitations of any scheme to classify antiarrhythmic agents, a shorthand that is useful in describing the major mechanisms of action is of some utility. Such a classification scheme was proposed in 1970 by Vaughan-Williams and later modified by Singh and Harrison. The classes of antiarrhythmic action are class I, local anesthetic effect due to blockade of Na^+ current; class II, interference with the action of catecholamines at the β -adrenergic receptor; class III, delay of repolarization due to inhibition of K^+ current or activation of depolarizing current; and class IV, interference with calcium conductance (Table 14-2). Class I antiarrhythmics have been further subdivided based on the kinetics and potency of Na^+ channel binding; class Ia agents (quinidine, procainamide) are those with moderate potency and intermediate kinetics; class Ib agents (lidocaine, mexiletine) are those with low potency and rapid kinetics; and class Ic drugs (flecainide, propafenone) are those with high potency and the slowest kinetics. The limitations of the Vaughan-Williams classification scheme include multiple actions of most drugs, overwhelming consideration of

TABLE 14-2

ANTIARRHYTHMIC DRUG ACTIONS

DRUG	CLASS ACTIONS				MISCELLANEOUS ACTION
	I	II	III	IV	
Quinidine	++		++		α -Adrenergic blockade
Procainamide	++		++		Ganglionic blockade
Flecainide	+++		+		
Propafenone	++	+			
Sotalol		++	+++		
Dofetilide			+++		
Amiodarone	++	++	+++	+	α -Adrenergic blockade
Ibutilide			+++		Na^+ channel activator

162 antagonism as a mechanism of action, and the fact that several agents have none of the four classes of action in the scheme.

CATHETER ABLATION The use of catheter ablation is based on the principle that there is a critical anatomic region of impulse generation or propagation that is required for the initiation and maintenance of cardiac arrhythmias. Destruction of such a critical region results in the elimination of the arrhythmia. The use of radiofrequency (RF) energy in clinical

medicine is nearly a century old. The first catheter ablation using a DC energy source was performed in the early 1980s by Scheinman and colleagues. By the early 1990s, RF had been adapted for use in catheter-based ablation in the heart (**Fig. 14-5**).

The RF band (300–30,000 kHz) is used to generate energy for several biomedical applications, including coagulation and cauterization of tissues. Energy of this frequency will not stimulate skeletal muscle or the heart and heats tissue by a

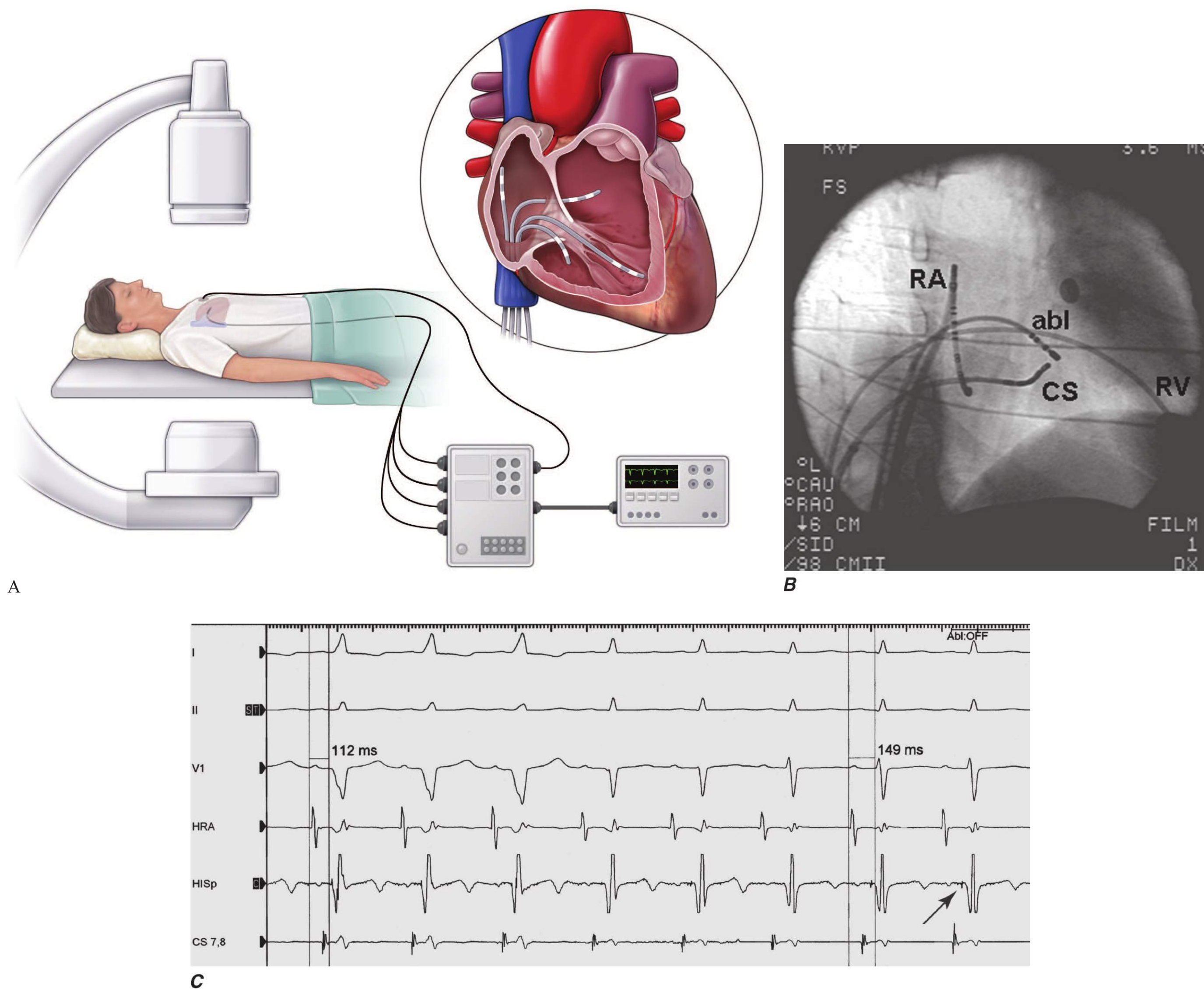


FIGURE 14-5

Catheter ablation of cardiac arrhythmias. A. A schematic of the catheter system and generator in a patient undergoing radiofrequency catheter ablation (RFCA); the circuit involves the catheter in the heart and a dispersive patch placed on the body surface (usually the back). The inset shows a diagram of the heart with a catheter located at the AV valve ring for ablation of an accessory pathway. B. A right anterior oblique fluoroscopic image of the catheter position for ablation of a left-sided accessory pathway. A catheter is placed in the atrial side of the mitral valve ring (abl) via a transseptal puncture. Other catheters are placed in

the coronary sinus (CS), in the right atrium (RA), and in the right ventricular (RV) apex to record local electrical activation. C. Body surface electrocardiogram recordings (I, II, V₁) and endocardial electrograms (HRA, high right atrium; HISp, proximal His bundle electrogram; CS 7, 8, recordings from poles 7 and 8 of a decapolar catheter placed in the coronary sinus) during RFCA of a left-sided accessory pathway in a patient with Wolf-Parkinson-White syndrome. The QRS narrows at the fourth complex; the arrow shows the His bundle electrogram, which becomes apparent with elimination of ventricular preexcitation over the accessory pathway.

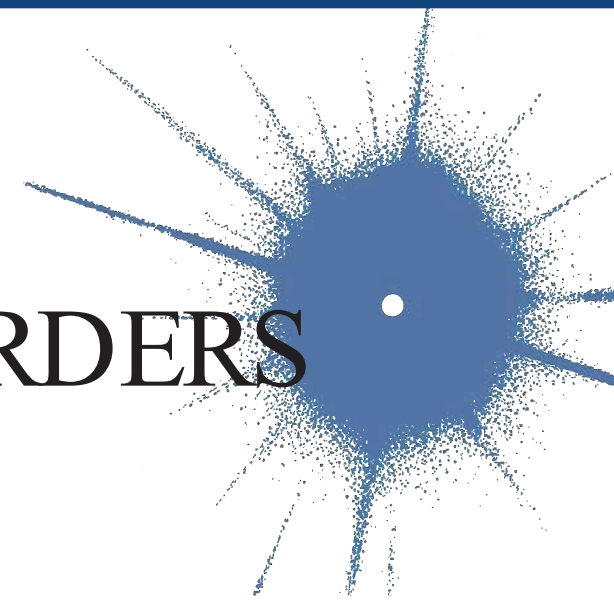
resistive mechanism, with the intensity of heating and tissue destruction being proportional to the delivered power. Alternative, less frequently used energy sources for catheter ablation of cardiac arrhythmias include microwaves (915 MHz or 2450 MHz), lasers, ultrasound, and freezing (cryoablation). Of these alternative ablation techniques, cryoablation is being used clinically with the most frequency, especially ablation in the region of the AVN. At temperatures just below 32°C, membrane ion transport is disrupted, producing depolarization of cells, decreased action potential amplitude and duration, and slowed conduction velocity (resulting in local conduction block)—all of which are reversible if the tissue is rewarmed in a timely fashion. Tissue cooling can be used for mapping and ablation. Cryomapping can be used to confirm the location of a desired ablation target, such as an accessory pathway in WPW syndrome, or can be used to determine the safety of ablation around the AVN by monitoring AV conduction during cooling. Another advantage of cryoablation is that once the catheter tip cools below freezing, it adheres to the tissue, increasing catheter stability independent of the rhythm or pacing.

DEVICE THERAPY Bradyarrhythmias due either to primary sinus node dysfunction or to atrioventricular conduction defects are readily treated through implantation of a permanent pacemaker. Clinical indications for pacemaker implantation often depend on the presence either of symptomatic bradycardia or of an unreliable endogenous escape rhythm and are more fully reviewed in **Chaps. 15 and 16**.

Ventricular tachyarrhythmias, particularly those occurring in the context of progressive structural heart diseases such as ischemic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, may recur despite therapy with antiarrhythmic drugs or catheter ablation. In appropriate candidates, implantation of an internal cardioverter-defibrillator (ICD) may reduce mortality rates from sudden cardiac death. In a subset of patients with congestive heart failure (CHF) and ventricular mechanical dyssynchrony, ICD or pacemaker platforms can be used to provide cardiac resynchronization therapy, typically through implantation of a left ventricular pacing lead. In patients with dyssynchronous CHF, such therapy has been shown to improve both morbidity and mortality rates.

CHAPTER 15

THE BRADYARRHYTHMIAS: DISORDERS OF THE SINOTRIAL NODE



David D. Spragg ■ Gordon F. Tomaselli

Electrical activation of the heart normally originates in the sinoatrial (SA) node, the predominant pacemaker. Other subsidiary pacemakers in the atrioventricular (AV) node, specialized conducting system, and muscle may initiate electrical activation if the SA node is dysfunctional or suppressed. Typically, subsidiary pacemakers discharge at a slower rate and, in the absence of an appropriate increase in stroke volume, may result in tissue hypoperfusion.

Spontaneous activation and contraction of the heart are a consequence of the specialized pacemaking tissue in these anatomic locales. As described in **Chap. 14**, action potentials in the heart are regionally heterogeneous. The action potentials in cells isolated from nodal tissue are distinct from those recorded from atrial and ventricular myocytes (**Fig. 15-1**). The complement of ionic currents present in nodal cells results in a less negative resting membrane potential compared with atrial or ventricular myocytes. Electrical diastole in nodal cells is characterized by slow diastolic depolarization (phase 4), which generates an action potential as the membrane voltage reaches threshold. The action potential upstrokes (phase 0) are slow compared with atrial or ventricular myocytes, being mediated by calcium rather than sodium current. Cells with properties of SA and AV nodal tissue are electrically connected to the remainder of the myocardium by cells with an electrophysiologic phenotype between that of nodal cells and that of atrial or ventricular myocytes. Cells in the SA node exhibit the most rapid phase 4 depolarization and thus are the dominant pacemakers in a normal heart.

Bradycardia results from a failure of either impulse initiation or impulse conduction. Failure of impulse initiation may be caused by depressed automaticity resulting from a slowing or failure of phase 4 diastolic

depolarization (**Fig. 15-2**), which may result from disease or exposure to drugs. Prominently, the autonomic nervous system modulates the rate of phase 4 diastolic depolarization and thus the firing rate of both primary (SA node) and subsidiary pacemakers. Failure of conduction of an impulse from nodal tissue to atrial or ventricular myocardium may produce bradycardia as a result of exit block. Conditions that alter the activation and connectivity of cells (e.g., fibrosis) in the heart may result in failure of impulse conduction.

SA node dysfunction and AV conduction block are the most common causes of pathologic bradycardia. SA node dysfunction may be difficult to distinguish from physiologic sinus bradycardia, particularly in the young. SA node dysfunction increases in frequency between the fifth and sixth decades of life and should be considered in patients with fatigue, exercise intolerance, or syncope and sinus bradycardia.

Permanent pacemaking is the only reliable therapy for symptomatic bradycardia in the absence of extrinsic and reversible etiologies such as increased vagal tone, hypoxia, hypothermia, and drugs (**Table 15-1**). Approximately 50% of the 150,000 permanent pacemakers implanted in the United States and 20–30% of the 150,000 of those in Europe were implanted for SA node disease.

STRUCTURE AND PHYSIOLOGY OF THE SA NODE

The SA node is composed of a cluster of small fusiform cells in the sulcus terminalis on the epicardial surface of the heart at the right atrial–superior vena caval junction, where they envelop the SA nodal artery. The SA node is structurally heterogeneous, but the central prototypic nodal cells have fewer distinct myofibrils than

The relative absence of inward rectifier potassium current (I_{K1}) accounts for the depolarized membrane potential; the slow upstroke of phase 0 results from the absence of available fast sodium current (I_{Na}) and is mediated by L-type calcium current (I_{Ca-L}); and phase 4 depolarization is a result of the aggregate activity of a number of ionic currents. Prominently, both L- and T-type (I_{Ca-T}) calcium currents, the pacemaker current (so-called funny current, or I_f) formed by hyperpolarization-activated cyclic nucleotide-gated channels, and the electrogenic sodium-calcium exchanger provide depolarizing current that is antagonized by delayed rectifier (I_{Kr}) and acetylcholine-gated (I_{KACh}) potassium currents. I_{Ca-L} , I_{Ca-T} , and I_f are modulated by β -adrenergic stimulation and I_{KACh} by vagal stimulation, explaining the exquisite sensitivity of diastolic depolarization to autonomic nervous system activity. The slow conduction within the SA node is explained by the absence of I_{Na} and poor electrical coupling of cells in the node, resulting from sizable amounts of interstitial tissue and a low abundance of gap junctions. The poor coupling allows for graded electrophysiologic properties within the node, with the peripheral transitional cells being silenced by electrotonic coupling to atrial myocardium.

ETIOLOGY OF SA NODAL DISEASE

SA nodal dysfunction has been classified as intrinsic or extrinsic. The distinction is important because extrinsic dysfunction is often reversible and generally should be corrected before pacemaker therapy is considered (Table 15-1). The most common causes of extrinsic SA node dysfunction are drugs and autonomic nervous system influences that suppress automaticity and/or compromise conduction. Other extrinsic causes include hypothyroidism, sleep apnea, and conditions likely to occur in critically ill patients such as hypothermia, hypoxia, increased intracranial pressure (Cushing's response), and endotracheal suctioning via activation of the vagus nerve.

Intrinsic sinus node dysfunction is degenerative and often is characterized pathologically by fibrous replacement of the SA node or its connections to the atrium. Acute and chronic coronary artery disease (CAD) may be associated with SA node dysfunction, although in the setting of acute myocardial infarction (MI; typically inferior), the abnormalities are transient. Inflammatory processes may alter SA node function, ultimately producing replacement fibrosis. Pericarditis, myocarditis, and rheumatic heart disease have been associated with SA nodal disease with sinus bradycardia, sinus arrest, and exit block. Carditis associated with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and mixed connective tissue disorders (MCTDs) may also affect SA node structure and function. Senile amyloidosis is an infiltrative disorder in patients typically in the

ninth decade of life; deposition of amyloid protein in the atrial myocardium can impair SA node function. Some SA node disease is iatrogenic and results from direct injury to the SA node during cardiothoracic surgery.

Rare heritable forms of sinus node disease have been described, and several have been characterized genetically. Autosomal dominant sinus node dysfunction in conjunction with supraventricular tachycardia (i.e., tachycardia-bradycardia variant of sick-sinus syndrome [SSS2]) has been linked to mutations in the pacemaker current (I_f) subunit gene HCN4 on chromosome 15. An autosomal recessive form of SSS1 with the prominent feature of atrial inexcitability and absence of P waves on the electrocardiogram (ECG) is caused by mutations in the cardiac sodium channel gene, SCN5A, on chromosome 3. Variants in myosin heavy chain 6 (MYH6) increase the susceptibility to SSS (SSS3). SA node dysfunction associated with myopia has been described but not genetically characterized. There are several neuromuscular diseases, including Kearns-Sayre syndrome (ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy) and myotonic dystrophy, that have a predilection for the conducting system and SA node.

SSS in both the young and the elderly is associated with an increase in fibrous tissue in the SA node. The onset of SSS may be hastened by coexisting disease, such as CAD, diabetes mellitus, hypertension, and valvular diseases and cardiomyopathies.

CLINICAL FEATURES OF SA NODE DISEASE

SA node dysfunction may be completely asymptomatic and manifest as an ECG anomaly such as sinus bradycardia; sinus arrest and exit block; or alternating supraventricular tachycardia, usually atrial fibrillation, and bradycardia. Symptoms associated with SA node dysfunction, in particular tachycardia-bradycardia syndrome, may be related to both slow and fast heart rates. For example, tachycardia may be associated with palpitations, angina pectoris, and heart failure, and bradycardia may be associated with hypotension, syncope, presyncope, fatigue, and weakness. In the setting of SSS, overdrive suppression of the SA node may result in prolonged pauses and syncope upon termination of the tachycardia. In many cases, symptoms associated with SA node dysfunction result from concomitant cardiovascular disease. A significant minority of patients with SSS develop signs and symptoms of heart failure that may be related to slow or fast heart rates.

One-third to one-half of patients with SA node dysfunction develop supraventricular tachycardia, usually atrial fibrillation or atrial flutter. The incidence of persistent atrial fibrillation in patients with SA node dysfunction increases with advanced age, hypertension, diabetes mellitus, left ventricular dilation, valvular

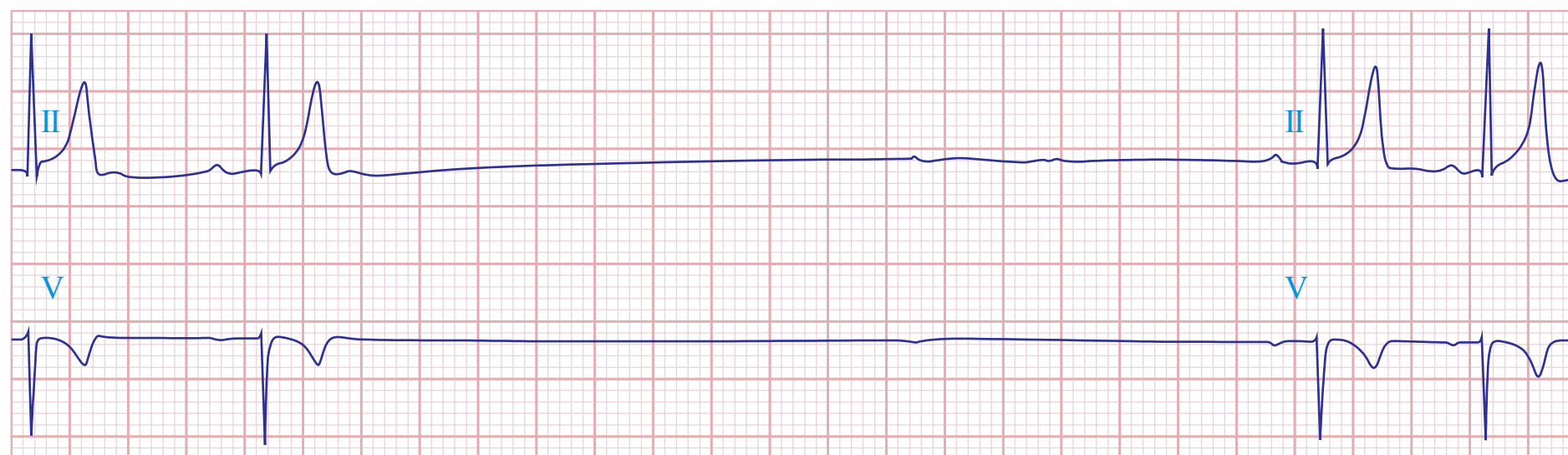


FIGURE 15-3

Sinus slowing and pauses on the electrocardiogram (ECG). The ECG is recorded during sleep in a young patient without heart disease. The heart rate before the pause is slow, and the PR interval is prolonged, consistent with an increase in vagal tone.

heart disease, and ventricular pacing. Remarkably, some symptomatic patients may experience an improvement in symptoms with the development of atrial fibrillation, presumably from an increase in their average heart rate. Patients with the tachycardia-bradycardia variant of SSS, similar to patients with atrial fibrillation, are at risk for thromboembolism, and those at greatest risk, including patients ≥ 65 years and patients with a prior history of stroke, valvular heart disease, left ventricular dysfunction, or atrial enlargement, should be treated with anticoagulants. Up to one-quarter of patients with SA node disease will have concurrent AV conduction disease, although only a minority will require specific therapy for high-grade AV block.

The natural history of SA node dysfunction is one of varying intensity of symptoms even in patients who present with syncope. Symptoms related to SA node dysfunction may be significant, but overall mortality usually is not compromised in the absence of other significant comorbid conditions. These features of the natural history need to be taken into account in considering therapy for these patients.

ELECTROCARDIOGRAPHY OF SA NODE DISEASE

The electrocardiographic manifestations of SA node dysfunction include sinus bradycardia, sinus pauses, sinus arrest, sinus exit block, tachycardia (in SSS), and

The P waves have a morphology consistent with sinus rhythm. The recording is from a two-lead telemetry system in which the tracing labeled II mimics frontal lead II and V represents Modified Central Lead 1, which mimics lead V_1 of the standard 12-lead ECG.

chronotropic incompetence. It is often difficult to distinguish pathologic from physiologic sinus bradycardia. By definition, sinus bradycardia is a rhythm driven by the SA node with a rate of <60 beats/min; sinus bradycardia is very common and typically benign. Resting heart rates <60 beats/min are very common in young healthy individuals and physically conditioned subjects. A sinus rate of <40 beats/min in the awake state in the absence of physical conditioning generally is considered abnormal. Sinus pauses and sinus arrest result from failure of the SA node to discharge, producing a pause without P waves visible on the ECG (Fig. 15-3). Sinus pauses of up to 3 s are common in awake athletes, and pauses of this duration or longer may be observed in asymptomatic elderly subjects. Intermittent failure of conduction from the SA node produces sinus exit block. The severity of sinus exit block may vary in a manner similar to that of AV block (Chap. 16). Prolongation of conduction from the sinus node will not be apparent on the ECG; second-degree SA block will produce intermittent conduction from the SA node and a regularly irregular atrial rhythm.

Type I second-degree SA block results from progressive prolongation of SA node conduction with intermittent failure of the impulses originating in the sinus node to conduct to the surrounding atrial tissue. Second-degree SA block appears on the ECG as an intermittent absence of P waves (Fig. 15-4). In type II second-degree SA block, there is no change in SA node conduction

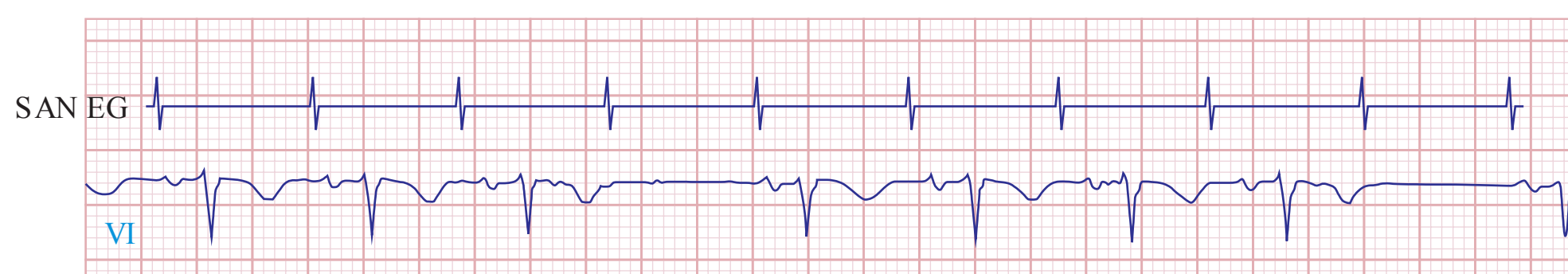


FIGURE 15-4

Mobitz type I SA nodal exit block. A theoretical SA node electrogram (SAN EG) is shown. Note that there is grouped beating producing a regularly irregular heart rhythm. The SA node EG rate is constant with progressive delay in exit from the node and

activation of the atria, inscribing the P wave. This produces subtly decreasing P-P intervals before the pause, and the pause is less than twice the cycle length of the last sinus interval.

before the pause. Complete or third-degree SA block results in no P waves on the ECG. Tachycardia-bradycardia syndrome is manifest as alternating sinus bradycardia and atrial tachyarrhythmias. Although atrial tachycardia, atrial flutter, and atrial fibrillation may be observed, the latter is the most common tachycardia. Chronotropic incompetence is the inability to increase the heart rate in response to exercise or other stress appropriately and is defined in greater detail below.

DIAGNOSTIC TESTING

SA node dysfunction is most commonly a clinical or electrocardiographic diagnosis. Sinus bradycardia or pauses on the resting ECG are rarely sufficient to diagnose SA node disease, and longer-term recording and symptom correlation generally are required. Symptoms in the absence of sinus bradyarrhythmias may be sufficient to exclude a diagnosis of SA node dysfunction.

Electrocardiographic recording plays a central role in the diagnosis and management of SA node dysfunction. Despite the limitations of the resting ECG, longer-term recording employing Holter or event monitors may permit correlation of symptoms with the cardiac rhythm. Many contemporary event monitors may be automatically triggered to record the ECG when certain programmed heart rate criteria are met. Implantable ECG monitors permit long-term recording (12–18 months) in particularly challenging patients.

Failure to increase the heart rate with exercise is referred to as chronotropic incompetence. This is alternatively defined as failure to reach 85% of predicted maximal heart rate at peak exercise or failure to achieve a heart rate >100 beats/min with exercise or a maximal heart rate with exercise less than two standard deviations below that of an age-matched control population. Exercise testing may be useful in discriminating chronotropic incompetence from resting bradycardia and may aid in the identification of the mechanism of exercise intolerance.

Autonomic nervous system testing is useful in diagnosing carotid sinus hypersensitivity; pauses >3 s are consistent with the diagnosis but may be present in asymptomatic elderly subjects. Determining the intrinsic heart rate (IHR) may distinguish SA node dysfunction from slow heart rates that result from high vagal tone. The normal IHR after administration of 0.2 mg/kg propranolol and 0.04 mg/kg atropine is $117.2 - (0.53 \times \text{age})$ in beats/min; a low IHR is indicative of SA disease.

Electrophysiologic testing may play a role in the assessment of patients with presumed SA node dysfunction and in the evaluation of syncope, particularly in the setting of structural heart disease. In this circumstance, electrophysiologic testing is used to rule out more malignant etiologies of syncope, such

as ventricular tachyarrhythmias and AV conduction block. There are several ways to assess SA node function invasively. They include the sinus node recovery time (SNRT), defined as the longest pause after cessation of overdrive pacing of the right atrium near the SA node (normal: <1500 ms or, corrected for sinus cycle length, <550 ms), and the sinoatrial conduction time (SACT), defined as one-half the difference between the intrinsic sinus cycle length and a noncompensatory pause after a premature atrial stimulus (normal <125 ms). The combination of an abnormal SNRT, an abnormal SACT, and a low IHR is a sensitive and specific indicator of intrinsic SA node disease.

TREATMENT Sinoatrial Node Dysfunction

Since SA node dysfunction is not associated with increased mortality rates, the aim of therapy is alleviation of symptoms. Exclusion of extrinsic causes of SA node dysfunction and correlation of the cardiac rhythm with symptoms is an essential part of patient management. Pacemaker implantation is the primary therapeutic intervention in patients with symptomatic SA node dysfunction. Pharmacologic considerations are important in the evaluation and management of patients with SA nodal disease. A number of drugs modulate SA node function and are extrinsic causes of dysfunction (Table 15-1). Beta blockers and calcium channel blockers increase SNRT in patients with SA node dysfunction, and antiarrhythmic drugs with class I and III action may promote SA node exit block. In general, such agents should be discontinued before decisions regarding the need for permanent pacing in patients with SA node disease are made. Chronic pharmacologic therapy for sinus bradyarrhythmias is limited. Some pharmacologic agents may improve SA node function; digitalis, for example, has been shown to shorten SNRT in patients with SA node dysfunction. Isoproterenol or atropine administered IV may increase the sinus rate acutely. Theophylline has been used both acutely and chronically to increase heart rate but has liabilities when used in patients with tachycardia-bradycardia syndrome, increasing the frequency of supraventricular tachyarrhythmias, and in patients with structural heart disease, increasing the risk of potentially serious ventricular arrhythmias. Currently, there is only a single randomized study of therapy for SA node dysfunction. In patients with resting heart rates <50 and >30 beats/min on a Holter monitor, patients who received dual-chamber pacemakers experienced significantly fewer syncopal episodes and had symptomatic improvement compared with patients randomized to theophylline or no treatment.

In certain circumstances, sinus bradycardia requires no specific treatment or only temporary rate support. Sinus bradycardia is common in patients with acute inferior or posterior MI and can be exacerbated by vagal activation induced by pain or the use of drugs such as morphine. Ischemia of

the SA nodal artery probably occurs in acute coronary syndromes more typically with involvement with the right coronary artery, and even with infarction, the effect on SA node function most often is transient.

Sinus bradycardia is a prominent feature of carotid sinus hypersensitivity and neurally mediated hypotension associated with vasovagal syncope that responds to pacemaker therapy. Carotid hypersensitivity with recurrent syncope or presyncope associated with a predominant cardioinhibitory component responds to pacemaker implantation. Several randomized trials have investigated the efficacy of permanent pacing in patients with drug-refractory vasovagal syncope, with mixed results. Although initial trials suggested that patients undergoing pacemaker implantation have fewer recurrences and a longer time to recurrence of symptoms, at least one follow-up study did not confirm these results.

PERMANENT PACEMAKERS Nomenclature and Complications The main therapeutic intervention in SA node dysfunction is permanent pacing. Since the first implementation of permanent pacing in the 1950s, many advances in technology have resulted in miniaturization, increased longevity of pulse generators, improvement in leads, and increased functionality. To better understand pacemaker therapy for bradycardias, it is important to be familiar with the fundamentals of pacemaking. Pacemaker modes and function are named using a five-letter code. The first letter indicates the chamber(s) that is paced (O, none; A, atrium; V, ventricle; D, dual; S, single), the second is the chamber(s) in which sensing occurs (O, none; A, atrium; V, ventricle; D, dual; S, single), the third is the response to a sensed event (O, none; I, inhibition; T, triggered; D, inhibition + triggered), the fourth refers to the programmability or rate response (R, rate responsive), and the fifth refers to the existence of antitachycardia functions if present (O, none; P, antitachycardia pacing; S, shock; D, pace + shock). Almost all modern pacemakers are multiprogrammable and have the capability for rate responsiveness using one of several rate sensors: activity or motion, minute ventilation, or QT interval. The most commonly programmed modes of implanted single- and dual-chamber pacemakers are VVIR and DDDR, respectively, although multiple modes can be programmed in modern pacemakers.

Although pacemakers are highly reliable, they are subject to a number of complications related to implantation and electronic function. In adults, permanent pacemakers are most commonly implanted with access to the heart by way of the subclavian–superior vena cava venous system. Rare, but possible, acute complications of transvenous pacemaker implantation include infection, hematoma, pneumothorax, cardiac perforation, diaphragmatic/phrenic nerve stimulation, and lead dislodgment. Limitations of chronic pacemaker therapy include infection, erosion, lead failure, and abnormalities resulting from inappropriate programming or interaction with the patient's native electrical cardiac function. Rotation of the pacemaker pulse generator in its subcutaneous pocket, either intentionally or inadvertently,

often referred to as “twiddler's syndrome,” can wrap the leads around the generator and produce dislodgment with failure to sense or pace the heart. The small size and light weight of contemporary pacemakers make this a rare complication.

Complications stemming from chronic cardiac pacing also result from disturbances in atrioventricular synchrony and/or left ventricular mechanical synchrony. Pacing modes that interrupt or fail to restore atrioventricular synchrony may lead to a constellation of signs and symptoms, collectively referred to as pacemaker syndrome, that include neck pulsation, fatigue, palpitations, cough, confusion, exertional dyspnea, dizziness, syncope, elevation in jugular venous pressure, canon A waves, and stigmata of congestive heart failure, including edema, rales, and a third heart sound. Right ventricular apical pacing can induce dyssynchronous activation of the left ventricle, leading to compromised left ventricular systolic function, mitral valve regurgitation, and the previously mentioned stigmata of congestive heart failure. Maintenance of AV synchrony can minimize the sequelae of pacemaker syndrome. Selection of pacing modes that minimize unnecessary ventricular pacing or implantation of a device capable of right and left ventricular pacing (biventricular pacing) can help minimize the deleterious consequences of pacing-induced mechanical dyssynchrony at the ventricular level.

Pacemaker Therapy in SA Node Dysfunction Pacing in SA nodal disease is indicated to alleviate symptoms of bradycardia. Consensus guidelines published by the American Heart Association (AHA)/American College of Cardiology/Heart Rhythm Society (ACC/HRS) outline the indications for the use of pacemakers and categorize them by class based on levels of evidence. Class I conditions are those for which there is evidence or consensus of opinion that therapy is useful and effective. In class II conditions, there is conflicting evidence or a divergence of opinion about the efficacy of a procedure or treatment; in class IIa conditions, the weight of evidence or opinion favors treatment; and in class IIb conditions, efficacy is less well established by the evidence or opinion of experts. In class III conditions, the evidence or weight of opinion indicates that the therapy is not efficacious or useful and may be harmful.

Class I indications for pacing in SA node dysfunction include documented symptomatic bradycardia, sinus node dysfunction–associated long-term drug therapy for which there is no alternative, and symptomatic chronotropic incompetence. Class IIa indications include those outlined previously in which sinus node dysfunction is suspected but not documented and for syncope of unexplained origin in the presence of major abnormalities of SA node dysfunction. Mildly symptomatic individuals with heart rates consistently <40 beats/min constitute a class IIb indication for pacing. Pacing is not indicated in patients with SA node dysfunction who do not have symptoms and in those in whom bradycardia is associated with the use of nonessential drugs ([Table 15-2](#)).

TABLE 15-2

SUMMARY OF GUIDELINES FOR PACEMAKER IMPLANTATION IN SA NODE DYSFUNCTION
Class I 1. SANode dysfunction with symptomatic bradycardia or sinus pause 2. Symptomatic SANode dysfunction as a result of essential long-term drug therapy with no acceptable alternatives 3. Symptomatic chronotropic incompetence 4. Atrial fibrillation with bradycardia and pauses >5 s
Class IIa 1. SANode dysfunction with heart rates <40 beats/min without a clear and consistent relationship between bradycardia and symptoms 2. SANode dysfunction with heart rates <40 beats/min on an essential long-term drug therapy with no acceptable alternatives, without a clear and consistent relationship between bradycardia and symptoms 3. Syncope of unknown origin when major abnormalities of SANode dysfunction are discovered or provoked by electrophysiologic testing
Class IIb 1. Mildly symptomatic patients with waking chronic heart rates <40 beats/min
Class III 1. SANode dysfunction in asymptomatic patients, even those with heart rates <40 beats/min 2. SANode dysfunction in which symptoms suggestive of bradycardia are not associated with a slow heart rate 3. SANode dysfunction with symptomatic bradycardia due to nonessential drug therapy

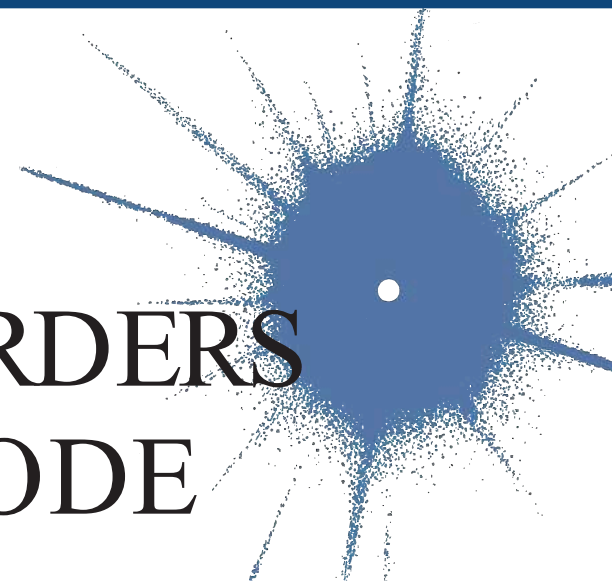
Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008 and CM Tracy et al: J Am Coll Cardiol 61:e6, 2013.

There is some controversy about the mode of pacing that should be employed in SA node disease. A number of randomized, single-blind trials of pacing mode have been performed. There are no trials that demonstrate an improvement in mortality rate with AV synchronous pacing compared with single-chamber pacing in SA node disease. In some of these studies, the incidence of atrial fibrillation and thromboembolic events was reduced with AV synchronous pacing. In trials of patients with dual-chamber pacemakers designed to compare single-chamber with dual-chamber pacing by crossover design, the need for AV synchronous pacing due to pacemaker syndrome was common. Pacing modes that preserve AV synchrony appear to be associated with a reduction in the incidence of atrial fibrillation and improved quality of life. Because of the low but finite incidence of AV conduction disease, patients with SA node dysfunction usually undergo dual-chamber pacemaker implantation.

Pacemaker Therapy in Carotid Sinus Hypersensitivity and Vasovagal Syncope Carotid sinus hypersensitivity, if accompanied by a significant cardioinhibitory component, responds well to pacing. In this circumstance, pacing is required only intermittently and single-chamber ventricular pacing is often sufficient. The mechanism of vasovagal syncope is incompletely understood but appears to involve activation of cardiac mechanoreceptors with consequent activation of neural centers that mediate vagal activation and withdrawal of sympathetic nervous system tone. Several randomized clinical trials have been performed in patients with drug-refractory vasovagal syncope, with some studies suggesting reduction in the frequency and the time to recurrent syncope in patients who were paced compared with those who were not. A recent follow-up study to one of those initial trials, however, found less convincing results, casting some doubt on the utility of pacing for vagally mediated syncope.

CHAPTER 16

THE BRADYARRHYTHMIAS: DISORDERS OF THE ATRIOVENTRICULAR NODE



David D. Spragg ■ Gordon F. Tomaselli

Impulses generated in the sinoatrial (SA) node or in ectopic atrial loci are conducted to the ventricles through the electrically and anatomically complex atrioventricular (AV) node. As described in **Chap. 15**, the electrophysiologic properties of nodal tissue are distinct from atrial and ventricular myocardium. Cells located in the AV node sit at a relatively higher resting membrane potential than surrounding atrial and ventricular myocytes, exhibit spontaneous depolarization during phase 4 of the action potential, and have slower phase 0 depolarization (mediated by calcium influx in nodal tissue) than that seen in ventricular tissue (mediated by sodium influx).

Bradycardia may occur when conduction across the AV node is compromised, resulting in ineffective ventricular rates, with the possibility of attendant symptoms, including fatigue, syncope, and (if subsidiary pacemaker activity is insufficient) even death. It is important to recognize that in the setting of disturbed AV conduction, SA activation and atrial systole may occur at normal or even accelerated rates, while ventricular activation is either slowed or nonexistent. Transient AV conduction block is common in the young and is most likely the result of high vagal tone found in up to 10% of young adults. Acquired and persistent failure of AV conduction is decidedly rare in healthy adult populations, with an estimated incidence of 200 per million population per year. In the setting of myocardial ischemia, aging and fibrosis, or cardiac infiltrative diseases, however, persistent AV block is much more common.

As with symptomatic bradycardia arising from SA node dysfunction, permanent pacing is the only reliable therapy for symptoms arising from AV conduction block. Approximately 50% of the 150,000 permanent pacemakers implanted in the United States and 70–80% of those in Europe are implanted for disorders of AV conduction.

STRUCTURE AND PHYSIOLOGY OF THE AV NODE

The AV conduction axis is structurally complex, involving the atria and ventricles as well as the AV node. Unlike the SA node, the AV node is a subendocardial structure originating in the transitional zone, which is composed of aggregates of cells in the posterior-inferior right atrium. Superior, medial, and posterior transitional atrionodal bundles converge on the compact AV node. The compact AV node ($\sim 1 \times 3 \times 5$ mm) is situated at the apex of the triangle of Koch, which is defined by the coronary sinus ostium posteriorly, the septal tricuspid valve annulus anteriorly, and the tendon of Todaro superiorly. The compact AV node continues as the penetrating AV bundle where it immediately traverses the central fibrous body and is in close proximity to the aortic, mitral, and tricuspid valve annuli; thus, it is subject to injury in the setting of valvular heart disease or its surgical treatment. The penetrating AV bundle continues through the annulus fibrosis and emerges along the ventricular septum adjacent to the membranous septum as the bundle of His. The right bundle branch (RBB) emerges from the distal AV bundle in a band that traverses the right ventricle (moderator band). In contrast, the left bundle branch (LBB) is a broad subendocardial sheet of tissue on the septal left ventricle. The Purkinje fiber network emerges from the RBB and LBB and extensively ramifies on the endocardial surfaces of the right and left ventricles, respectively.

The blood supply to the penetrating AV bundle is from the AV nodal artery and first septal perforator of the left anterior descending coronary artery. The bundle branches also have a dual blood supply from the septal perforators of the left anterior descending coronary artery and branches of the posterior descending coronary artery. The AV node is highly innervated

172 with postganglionic sympathetic and parasympathetic nerves. The bundle of His and distal conducting system are minimally influenced by autonomic tone.

The cells that constitute the AV node complex are heterogeneous with a range of action potential profiles. In the transitional zones, the cells have an electrical phenotype between those of atrial myocytes and cells of the compact node (see Fig. 15-1). Atrionodal transitional connections may exhibit decremental conduction, defined as slowing of conduction with increasingly rapid rates of stimulation. Fast and slow AV nodal pathways have been described, but it is controversial whether these two types of pathway are anatomically distinct or represent functional heterogeneities in different regions of the AV nodal complex. Myocytes that constitute the compact node are depolarized (resting membrane potential ~ -60 mV) and exhibit action potentials with low amplitudes, slow upstrokes of phase 0 (<10 V/s), and phase 4 diastolic depolarization; high-input resistance; and relative insensitivity to external $[K^+]$. The action potential phenotype is explained by the complement of ionic currents expressed. AV nodal cells lack a robust inward rectifier potassium current (I_{K1}) and fast sodium current (I_{Na}); L-type calcium current (I_{Ca-L}) is responsible for phase 0; and phase 4 depolarization reflects the composite activity of the depolarizing currents—funny current (I_f), I_{Ca-L} , T-type calcium current (I_{Ca-T}), and sodium calcium exchanger current (I_{NCX})—and the repolarizing currents—delayed rectifier (I_{Kr}) and acetylcholine-gated (I_{KACh}) potassium currents. Electrical coupling between cells in the AV node is tenuous due to the relatively sparse expression of gap junction channels (predominantly connexin-40) and increased extracellular volume.

The His bundle and the bundle branches are insulated from ventricular myocardium. The most rapid conduction in the heart is observed in these tissues. The action potentials exhibit very rapid upstrokes (phase 0), prolonged plateaus (phase 2), and modest automaticity (phase 4 depolarization). Gap junctions, composed largely of connexin-40, are abundant, but bundles are poorly connected transversely to ventricular myocardium.

ETIOLOGY OF AV CONDUCTION DISEASE

Conduction block from the atrium to the ventricle can occur for a variety of reasons in a number of clinical situations, and AV conduction block may be classified in a number of ways. The etiologies may be functional or structural, in part analogous to extrinsic and intrinsic causes of SA nodal dysfunction. The block may be classified by its severity from first to third degree or complete AV block or by the location of block within the AV conduction system. Table 16-1 summarizes

TABLE 16-1
ETIOLOGIES OF ATRIOVENTRICULAR BLOCK

Autonomic	
Carotid sinus hypersensitivity	Vasovagal
Metabolic/Endocrine	
Hyperkalemia	Hypothyroidism
Hypermagnesemia	Adrenal insufficiency
Drug-Related	
Beta blockers	Adenosine
Calcium channel blockers	Antiarrhythmics (class I and III)
Digitalis	Lithium
Infectious	
Endocarditis	Tuberculosis
Lyme disease	Diphtheria
Chagas' disease	Toxoplasmosis
Syphilis	
Heritable/Congenital	
Congenital heart disease	Facioscapulohumeral MD, OMIM #158900 (4q35)
Maternal SLE	Emery-Dreifuss MD, OMIM #310300 (Xq28)
Kearns-Sayre syndrome, OMIM #530000	Progressive familial heart block, type IA OMIM #113900 (3p21)
Myotonic dystrophy Type 1, OMIM #160900 (19q13.2-13.3)	Progressive familial heart block, type IB, OMIM #604559 (19q13.32)
Type 2, OMIM #602668 (3q13.3-q24)	Progressive familial heart block, type II, OMIM #140400
Inflammatory	
SLE	MCTD
Rheumatoid arthritis	Scleroderma
Infiltrative	
Amyloidosis	Hemochromatosis
Sarcoidosis	
Neoplastic/Traumatic	
Lymphoma	Radiation
Mesothelioma	Catheter ablation
Melanoma	
Degenerative	
Lev's disease	Lenègre's disease
Coronary Artery Disease	
Acute MI	

Abbreviations: MCTD, mixed connective tissue disease; MI, myocardial infarction; OMIM, Online Mendelian Inheritance in Man (database; designations: #, phenotypic description, molecular basis known; %, phenotypic description); SLE, systemic lupus erythematosus.

the etiologies of AV conduction block. Those that are functional (autonomic, metabolic/endocrine, and drug-related) tend to be reversible. Most other etiologies produce structural changes, typically fibrosis, in segments of the AV conduction axis that are generally permanent. Heightened vagal tone during sleep or in well-conditioned individuals can be associated with all grades of AV block. Carotid sinus hypersensitivity, vasovagal syncope, and cough and micturition syncope may be associated with SA node slowing and AV conduction block. Transient metabolic and endocrinologic disturbances as well as a number of pharmacologic agents also may produce reversible AV conduction block.

Several infectious diseases have a predilection for the conducting system. Lyme disease may involve the heart in up to 50% of cases; 10% of patients with Lyme carditis develop AV conduction block, which is generally reversible but may require temporary pacing support. Chagas' disease, which is common in Latin America, and syphilis may produce more persistent AV conduction disturbances. Some autoimmune and infiltrative diseases may produce AV conduction block, including systemic lupus erythematosus (SLE), rheumatoid arthritis, mixed connective tissue disease, scleroderma, amyloidosis (primary and secondary), sarcoidosis, and hemochromatosis; rare malignancies also may impair AV conduction.

Idiopathic progressive fibrosis of the conduction system is one of the more common and degenerative causes of AV conduction block. Aging is associated with degenerative changes in the summit of the ventricular septum, central fibrous body, and aortic and mitral annuli and has been described as "sclerosis of the left cardiac skeleton." The process typically begins in the fourth decade of life and may be accelerated by atherosclerosis, hypertension, and diabetes mellitus. Accelerated forms of progressive familial heart block have been identified in families with mutations in the cardiac sodium channel gene (SCN5A) and other loci that have been mapped to chromosomes 1 and 19.

AV conduction block has been associated with heritable neuromuscular diseases, including the nucleotide repeat disease myotonic dystrophy, the mitochondrial myopathy Kearns-Sayre syndrome, and several of the monogenic muscular dystrophies. Congenital AV block may be observed in complex congenital cardiac anomalies (**Chap. 22**), such as transposition of the great arteries, ostium primum atrial septal defects (ASDs), ventricular septal defects (VSDs), endocardial cushion defects, and some single-ventricle defects. Congenital AV block in the setting of a structurally normal heart has been seen in children born to mothers with SLE. Iatrogenic AV block may occur during mitral or aortic valve surgery, rarely in the setting of thoracic radiation, and as a consequence of catheter ablation. AV block is

a decidedly rare complication of the surgical repair of VSDs or ASDs but may complicate repairs of transposition of the great arteries.

Coronary artery disease may produce transient or persistent AV block. In the setting of coronary spasm, ischemia, particularly in the right coronary artery distribution, may produce transient AV block. In acute myocardial infarction (MI), AV block transiently develops in 10–25% of patients; most commonly, this is first- or second-degree AV block, but complete heart block (CHB) may also occur. Second-degree and higher-grade AV block tends to occur more often in inferior than in anterior acute MI; however, the level of block in inferior MI tends to be in the AV node with more stable, narrow escape rhythms. In contrast, acute anterior MI is associated with block in the distal AV nodal complex, His bundle, or bundle branches and results in wide complex, unstable escape rhythms and a worse prognosis with high mortality rates.

ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY OF AV CONDUCTION BLOCK

AV conduction block typically is diagnosed electrocardiographically, which characterizes the severity of the conduction disturbance and allows one to draw inferences about the location of the block. AV conduction block manifests as slow conduction in its mildest forms and failure to conduct, either intermittent or persistently, in more severe varieties. First-degree AV block (PR interval >200 ms) is a slowing of conduction through the AV junction (**Fig. 16-1**). The site of delay is typically in the AV node but may be in the atria, bundle of His, or His-Purkinje system. A wide QRS is suggestive of delay in the distal conduction system, whereas a narrow QRS suggests delay in the AV node proper or, less commonly, in the bundle of His. In second-degree AV block there is an intermittent failure of electrical impulse conduction from atrium to ventricle. Second-degree AV block is subclassified as Mobitz type I (Wenckebach) or Mobitz type II. The periodic failure of conduction in Mobitz type I block is characterized by a progressively lengthening PR interval, shortening of the RR interval, and a pause that is less than two times the immediately preceding RR interval on the electrocardiogram (ECG). The ECG complex after the pause exhibits a shorter PR interval than that immediately preceding the pause (**Fig. 16-2**). This ECG pattern most often arises because of decremental conduction of electrical impulses in the AV node.

It is important to distinguish type I from type II second-degree AV nodal block because the latter has more serious prognostic implications. Type II second-degree AV block is characterized by

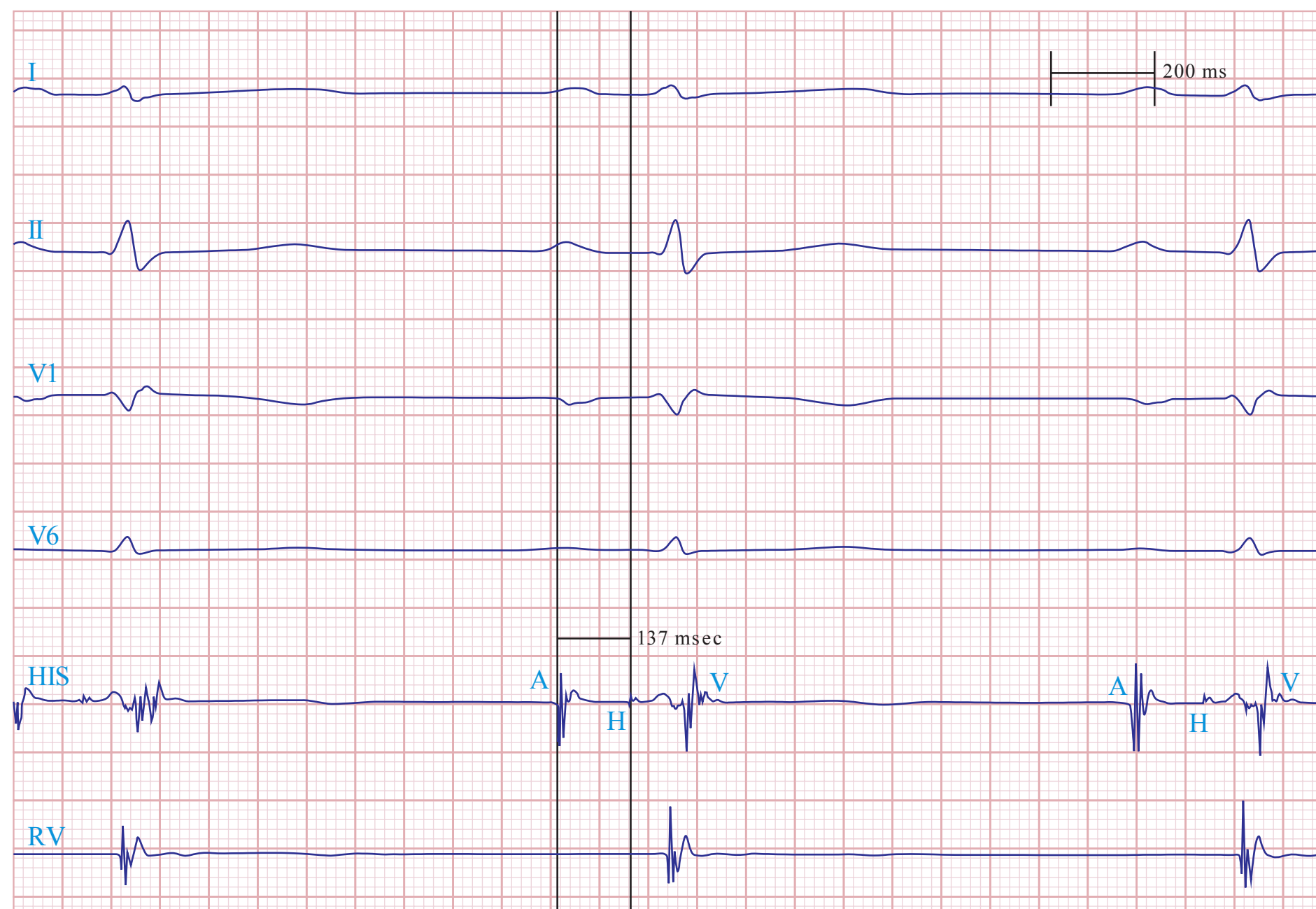


FIGURE 16-1

First-degree AV block with slowing of conduction in the AV node as indicated by the prolonged atrial-to-His bundle electrogram (AH) interval, in this case 157 ms. The His bundle-to-earliest ventricular activation on the surface ECG (HV) interval is normal. The normal HV interval suggests normal

conduction below the AV node to the ventricle. I and V_1 are surface ECG leads, and HIS is the recording of the endocavitary electrogram at the His bundle position. A, H, and V are labels for the atrial, His bundle, and right ventricular electrograms, respectively.

intermittent failure of conduction of the P wave without changes in the preceding PR or RR intervals. When AV block is 2:1, it may be difficult to distinguish type I from type II block. Type II second-degree AV block typically occurs in the distal or infra-His conduction system, is often associated with intraventricular conduction delays (e.g., bundle branch block), and is more likely to proceed to higher grades of AV block than is type I second-degree AV block. Second-degree AV block (particularly type II) may be associated with a series of nonconducted P waves, referred to as paroxysmal AV block (Fig. 16-3), and implies significant conduction system disease and is an indication for permanent pacing. Complete failure

of conduction from atrium to ventricle is referred to as complete or third-degree AV block. AV block that is intermediate between second degree and third degree is referred to as high-grade AV block and, as with CHB, implies advanced AV conduction system disease. In both cases, the block is most often distal to the AV node, and the duration of the QRS complex can be helpful in determining the level of the block. In the absence of a preexisting bundle branch block, a wide QRS escape rhythm (Fig. 16-4B) implies a block in the distal His or bundle branches; in contrast, a narrow QRS rhythm implies a block in the AV node or proximal His and an escape rhythm originating in the AV junction (Fig. 16-4A). Narrow QRS escape rhythms are typically faster



FIGURE 16-2

Mobitz type I second-degree AV block. The PR interval prolongs before the pause, as shown in the ladder diagram. The ECG pattern results from slowing of conduction in the AV node.

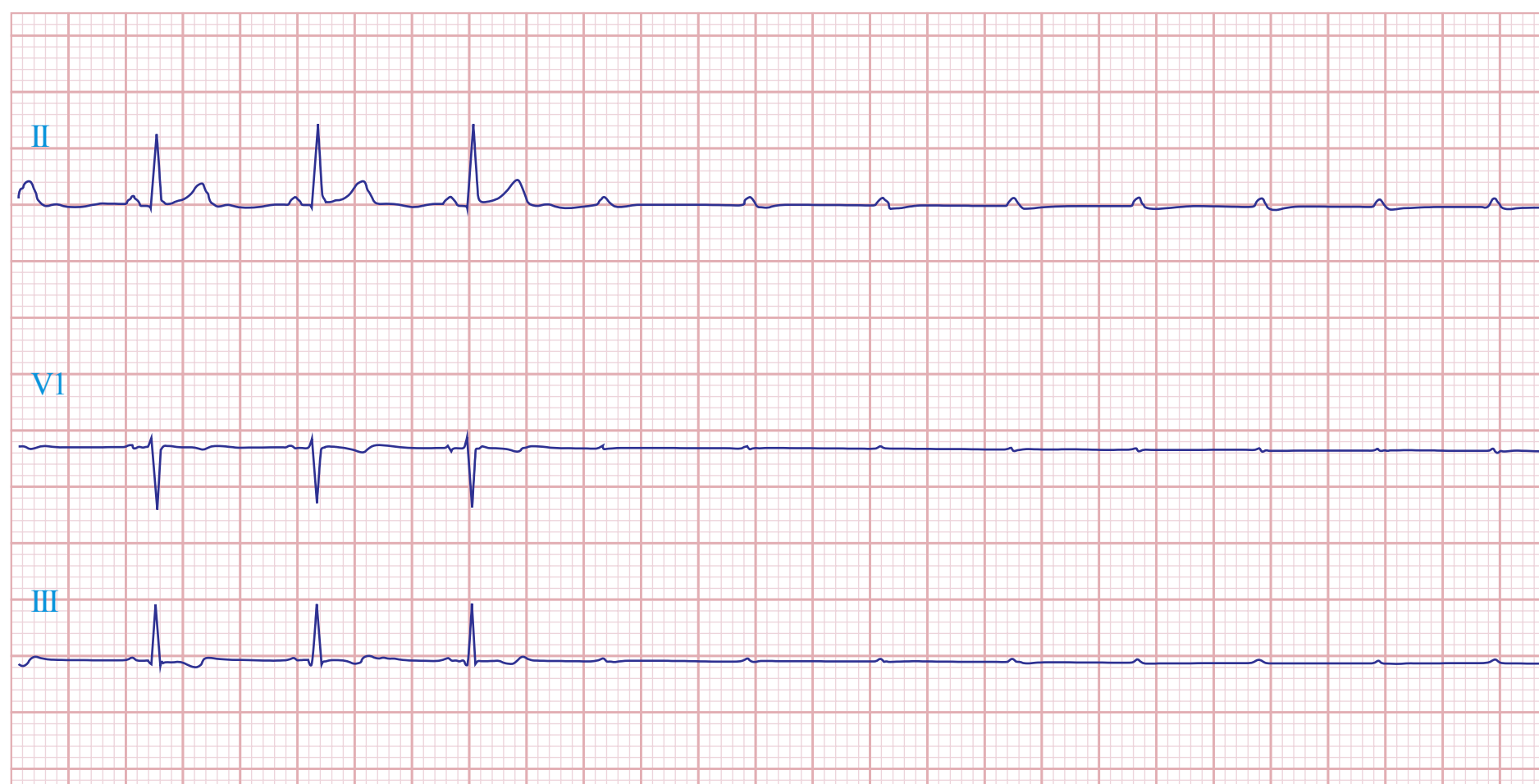


FIGURE 16-3

Paroxysmal AV block. Multiple nonconducted P waves after a period of sinus bradycardia with a normal PR interval. This implies

significant conduction system disease, requiring permanent pacemaker implantation.

and more stable than wide QRS escape rhythms and originate more proximally in the AV conduction system.

DIAGNOSTIC TESTING

Diagnostic testing in the evaluation of AV block is aimed at determining the level of conduction block, particularly in asymptomatic patients, since the prognosis and therapy depend on whether the block is in or below the AV node. Vagal maneuvers, carotid sinus massage, exercise, and administration of drugs such as atropine and isoproterenol may be diagnostically informative. Owing to the differences in the innervation of the AV node and infranodal conduction system, vagal stimulation and carotid sinus massage slow conduction in the AV node but have less of an effect on infranodal tissue and may even improve conduction due to a reduced rate of activation of distal tissues. Conversely,

atropine, isoproterenol, and exercise improve conduction through the AV node and impair infranodal conduction. In patients with congenital CHB and a narrow QRS complex, exercise typically increases heart rate; by contrast, those with acquired CHB, particularly with wide QRS, do not respond to exercise with an increase in heart rate.

Additional diagnostic evaluation, including electrophysiologic testing, may be indicated in patients with syncope and suspected high-grade AV block. This is particularly relevant if noninvasive testing does not reveal the cause of syncope or if the patient has structural heart disease with ventricular tachyarrhythmias as a cause of symptoms. Electrophysiologic testing provides more precise information regarding the location of AV conduction block and permits studies of AV conduction under conditions of pharmacologic stress and exercise. Recording of the His bundle electrogram

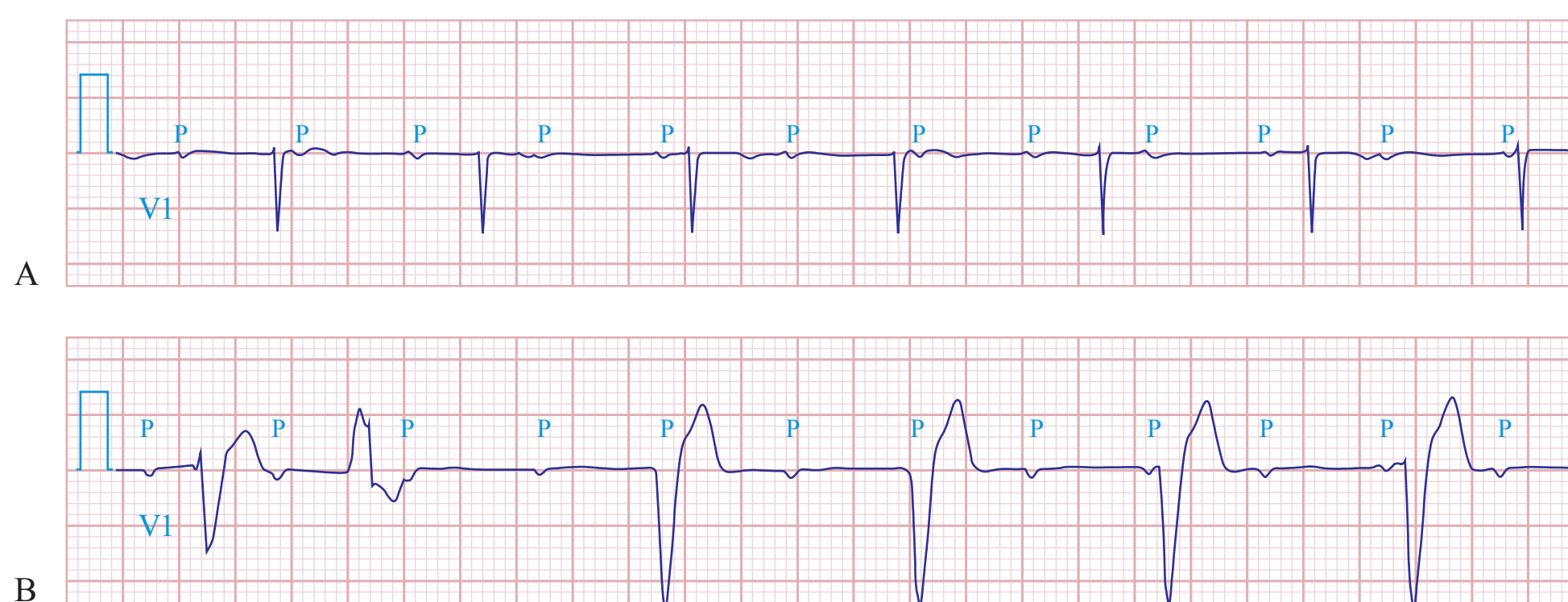


FIGURE 16-4

High-grade AV block. A. Multiple nonconducted P waves with a regular narrow complex QRS escape rhythm probably emanating from the AV junction. B. A wide complex QRS escape and a

single premature ventricular contraction. In both cases, there is no consistent temporal relationship between the P waves and QRS complexes.

by a catheter positioned at the superior margin of the tricuspid valve annulus provides information about conduction at all levels of the AV conduction axis. A properly recorded His bundle electrogram reveals local atrial activity, the His electrogram, and local ventricular activation; when it is monitored simultaneously with recorded body surface electrocardiographic traces, intraatrial, AV nodal, and infranodal conduction times can be assessed (Fig. 16-1). The time from the most rapid deflection of the atrial electrogram in the His bundle recording to the His electrogram (AH interval) represents conduction through the AV node and is normally <130 ms. The time from the His electrogram to the earliest onset of the QRS on the surface ECG (HV interval) represents the conduction time through the His-Purkinje system and is normally ≤ 55 ms.

Rate stress produced by pacing can unveil abnormal AV conduction. Mobitz I second-degree AV block at short atrial paced cycle lengths is a normal response. However, when it occurs at atrial cycle lengths >500 ms (<120 beats/min) in the absence of high vagal tone, it is abnormal. Typically, type I second-degree

AV block is associated with prolongation of the AH interval, representing conduction slowing and block in the AV node. AH prolongation occasionally is due to the effect of drugs (beta blockers, calcium channel blockers, digitalis) or increased vagal tone. Atropine can be used to reverse high vagal tone; however, if AH prolongation and AV block at long pacing cycle lengths persists, intrinsic AV node disease is likely. Type II second-degree block is typically infranodal, often in the His-Purkinje system. Block below the node with prolongation of the HV interval or a His bundle electrogram with no ventricular activation (Fig. 16-5) is abnormal unless it is elicited at fast pacing rates or short coupling intervals with extra stimulation. It is often difficult to determine the type of second-degree AV block when 2:1 conduction is present; however, the finding of a His bundle electrogram after every atrial electrogram indicates that block is occurring in the distal conduction system.

Intracardiac recording at electrophysiologic study that reveals prolongation of conduction through the His-Purkinje system (i.e., long HV interval) is

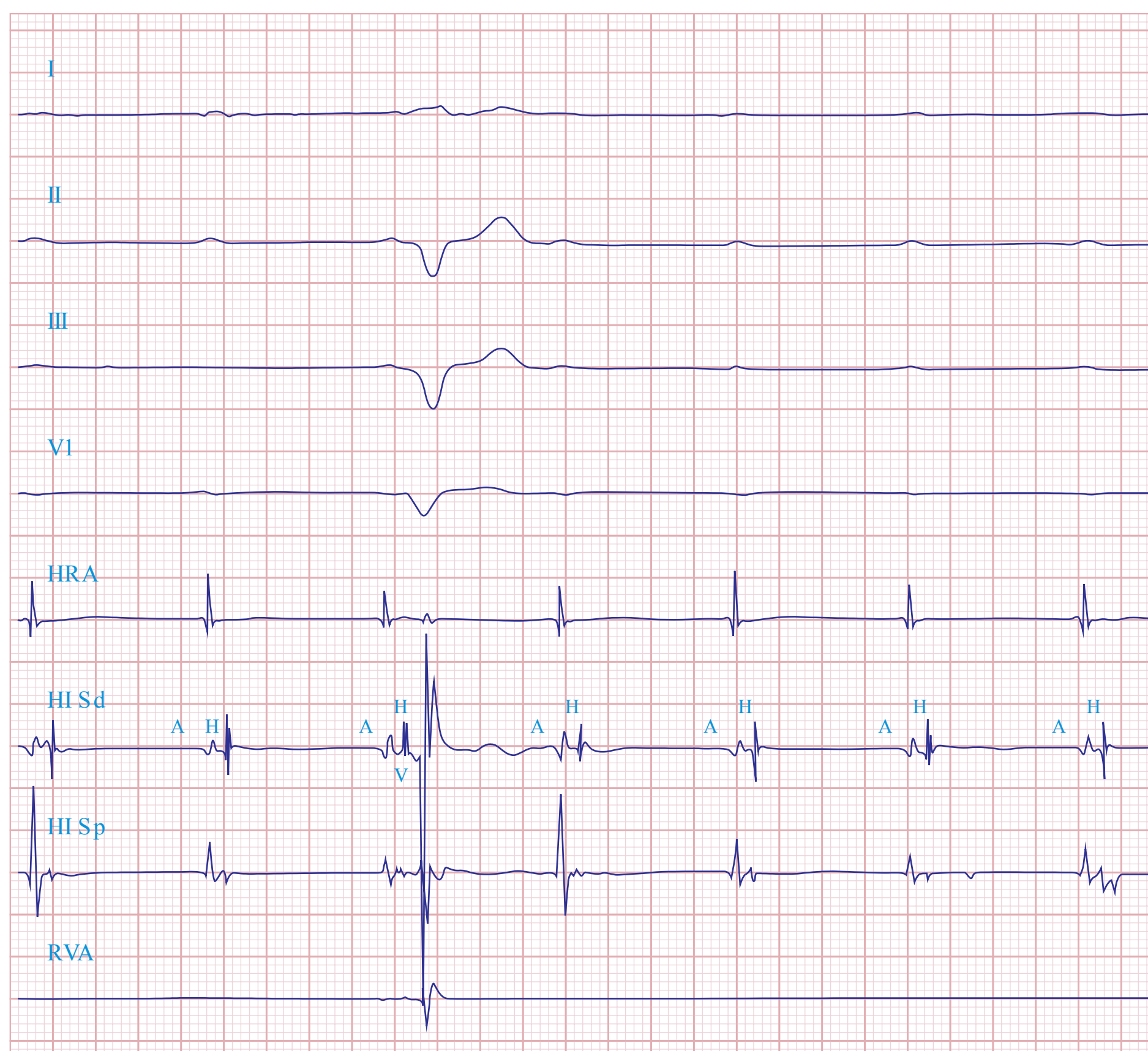


FIGURE 16-5

High-grade AV block below the His. The AH interval is normal and is not changing before the block. Atrial and His bundle electrograms are recorded consistent with block below the distal AV junction. I, II, III, and V₁ are surface ECG leads. HISp, HISd, and RVA

are the proximal HIS, distal HIS, and right ventricular apical electrical recordings, respectively. A, H, and V represent the atrial, His, and ventricular electrograms on the His bundle recording, respectively. (Tracing courtesy of Dr. Joseph Marine; with permission.)

associated with an increased risk of progression to higher grades of block and is generally an indication for pacing. In the setting of bundle branch block, the HV interval may reveal the condition of the unblocked bundle and the prognosis for developing more advanced AV conduction block. Prolongation of the HV interval in patients with asymptomatic bundle branch block is associated with an increased risk of developing higher-grade AV block. The risk increases with greater prolongation of the HV interval such that in patients with an HV interval >100 ms, the annual incidence of complete AV block approaches 10%, indicating a need for pacing. In patients with acquired CHB, even if intermittent, there is little role for electrophysiologic testing, and pacemaker implantation is almost always indicated.

TREATMENT Management of AV Conduction Block

Temporary or permanent artificial pacing is the most reliable treatment for patients with symptomatic AV conduction system disease. However, exclusion of reversible causes of AV block and the need for temporary heart rate support based on the hemodynamic condition of the patient are essential considerations in each patient. Correction of electrolyte derangements and ischemia, inhibition of excessive vagal tone, and withholding of drugs with AV nodal blocking properties may increase the heart rate. Adjunctive pharmacologic treatment with atropine or isoproterenol may be useful if the block is in the AV node. Since most pharmacologic treatment may take some time to initiate and become effective, temporary pacing may be necessary. The most expeditious technique is the use of transcutaneous pacing, where pacing patches are placed anteriorly over the cardiac apex (cathode) and posteriorly between the spine and the scapula or above the right nipple (anode). Acutely, transcutaneous pacing is highly effective, but its duration is limited by patient discomfort and longer-term failure to capture the ventricle owing to changes in lead impedance. If a patient requires more than a few minutes of pacemaker support, transvenous temporary pacing should be instituted. Temporary pacing leads can be placed from the jugular or subclavian venous system and advanced to the right ventricle, permitting stable temporary pacing for many days, if necessary. In most circumstances, in the absence of prompt resolution, conduction block distal to the AV node requires permanent pacemaking.

Pacemakers in AV Conduction Disease There are no randomized trials that evaluate the efficacy of pacing in patients with AV block, as there are no reliable therapeutic alternatives for AV block and untreated high-grade AV block is potentially lethal. The consensus guidelines for pacing in acquired AV conduction block in adults provide a general outline for situations in which pacing is indicated (**Table 16-2**). Pacemaker implantation should be performed in any patient with symptomatic bradycardia and irreversible second- or third-degree AV

TABLE 16-2

GUIDELINE SUMMARY FOR PACEMAKER IMPLANTATION IN ACQUIRED AV BLOCK

Class I

1. Third-degree or high-grade AVblock at any anatomic level associated with:
 - a. Symptomatic bradycardia
 - b. Essential drug therapy that produces symptomatic bradycardia
 - c. Periods of asystole >3 s or any escape rate <40 beats/min while awake, or an escape rhythm originating below the AVnode
 - d. Postoperative AVblock not expected to resolve
 - e. Catheter ablation of the AVjunction
 - f. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy, regardless of the presence of symptoms
2. Second-degree AVblock with symptomatic bradycardia
3. Type II second-degree AVblock with a wide QRS complex with or without symptoms
4. Exercise-induced second- or third-degree AVblock in the absence of ischemia
5. Atrial fibrillation with bradycardia and pauses >5 s

Class IIa

1. Asymptomatic third-degree AVblock regardless of level
2. Asymptomatic type II second-degree AVblock with a narrow QRS complex
3. Asymptomatic type II second-degree AVblock with block within or below the His at electrophysiologic study
4. First- or second-degree AVblock with symptoms similar to pacemaker syndrome

Class IIb

1. AVblock in the setting of drug use/toxicity, when the block is expected to recur even with drug discontinuation
2. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of AVblock regardless of the presence of symptoms

Class III

1. Asymptomatic first-degree AVblock
2. Asymptomatic type I second-degree AVblock at the AVnode level
3. AVblock that is expected to resolve or is unlikely to recur (Lyme disease, drug toxicity)

Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

block, regardless of the cause or level of block in the conducting system. Symptoms may include those directly related to bradycardia and low cardiac output or to worsening heart failure, angina, or intolerance to an essential medication. Pacing in patients with asymptomatic AV block should be individualized; situations in which pacing should be considered are patients with acquired CHB, particularly in the setting of cardiac enlargement; left ventricular dysfunction; and waking heart rates ≤ 40 beats/min. Patients who have asymptomatic second-degree AV block of either type should be considered

178 for pacing if the block is demonstrated to be intra- or infra-His or is associated with a wide QRS complex. Pacing may be indicated in asymptomatic patients in special circumstances, in patients with profound first-degree AV block and left ventricular dysfunction in whom a shorter AV interval produces hemodynamic improvement, and in the setting of milder forms of AV conduction delay (first-degree AV block, intra-ventricular conduction delay) in patients with neuromuscular diseases that have a predilection for the conduction system, such as myotonic dystrophy and other muscular dystrophies, and Kearns-Sayre syndrome.

Pacemaker Therapy in Myocardial Infarction AV block in acute MI is often transient, particularly in inferior infarction. The circumstances in which pacing is indicated in acute MI are persistent second-or third-degree AV block, particularly if symptomatic, and transient second-or third-degree AV block associated with bundle branch block (Table 16-3). Pacing is generally not indicated in the setting of transient AV block in the absence of intraventricular conduction delays or in the presence of fascicular block or first-degree AV block that develops in the setting of preexisting bundle branch block. Fascicular blocks that develop in acute MI in the absence of other forms of AV block also do not require pacing (Table 16-3 and Table 16-4).

Pacemaker Therapy in Bifascicular and Trifascicular Block Distal forms of AV conduction block may require pacemaker implantation in certain clinical settings. Patients with bifascicular or trifascicular block and symptoms, particularly syncope

TABLE 16-3

GUIDELINE SUMMARY FOR PACEMAKER IMPLANTATION IN AV CONDUCTION BLOCK IN ACUTE MYOCARDIAL INFARCTION (AMI)
Class I
1. Persistent second-degree AVblock in the His-Purkinje system with bilateral bundle branch block or third-degree block within or below the His after AMI
2. Transient advanced (second-or third-degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiologic study may be necessary
3. Persistent and symptomatic second-or third-degree AVblock
Class IIb
1. Persistent second- or third-degree AVblock at the AVnode level
Class III
1. Transient AVblock in the absence of intraventricular conduction defects
2. Transient AVblock in the presence of isolated left anterior fascicular block
3. Acquired left anterior fascicular block in the absence of AV block
4. Persistent first-degree AVblock in the presence of bundle branch block that is old or age-indeterminate

Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

TABLE 16-4

INDICATIONS FOR PACEMAKER IMPLANTATION IN CHRONIC BIFASCICULAR AND TRIFASCICULAR BLOCK
Class I
1. Intermittent third-degree AVblock
2. Type II second-degree AVblock
3. Alternating bundle branch block
Class IIa
1. Syncope not demonstrated to be due to AVblock when other likely causes (e.g., ventricular tachycardia) have been excluded
2. Incidental finding at electrophysiologic study of a markedly prolonged HV interval (>100 ms) in asymptomatic patients
3. Incidental finding at electrophysiologic study of pacing-induced infra-His block that is not physiologic
Class IIb
1. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of fascicular block regardless of the presence of symptoms, because there may be unpredictable progression of AVconduction disease
Class III
1. Fascicular block without AVblock or symptoms
2. Fascicular block with first-degree AVblock without symptoms

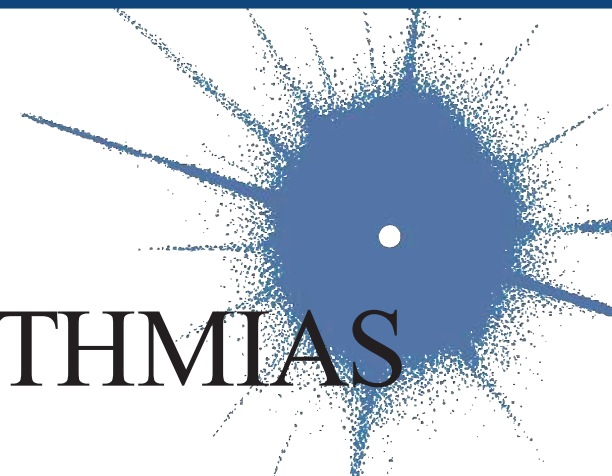
Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

that is not attributable to other causes, should undergo pacemaker implantation. Pacemaking is indicated in asymptomatic patients with bifascicular or trifascicular block who experience intermittent third-degree, type II second-degree AV block or alternating bundle branch block. In patients with fascicular block who are undergoing electrophysiologic study, a markedly prolonged HV interval or block below the His at long cycle lengths also may constitute an indication for permanent pacing. Patients with fascicular block and the neuromuscular diseases previously described should also undergo pacemaker implantation (Table 16-4).

SELECTION OF PACING MODE In general, a pacing mode that maintains AV synchrony reduces complications of pacing such as pacemaker syndrome and pacemaker-mediated tachycardia. This is particularly true in younger patients; the importance of dual-chamber pacing in the elderly, however, is not well established. Several studies have failed to demonstrate a difference in mortality rate in older patients with AV block treated with a single-(VVI) compared with a dual-(DDD) chamber pacing mode. In some of the studies that randomized pacing mode, the risk of chronic atrial fibrillation and stroke risk decreased with physiologic pacing. In patients with sinus rhythm and AV block, the very modest increase in risk with dual-chamber pacemaker implantation appears to be justified to avoid the possible complications of single-chamber pacing.

CHAPTER 17

SUPRAVENTRICULAR TACHYARRHYTHMIAS



Gregory F. Michaud ■ William G. Stevenson

Supraventricular tachyarrhythmias originate from or are dependent on conduction through the atrium or atrioventricular (AV) node to the ventricles. Most produce narrow QRS-complex tachycardia (QRS duration <120 ms) characteristic of ventricular activation over the Purkinje system. Conduction block in the left or right bundle branch or activation of the ventricles from an accessory pathway produces a wide QRS complex during supraventricular tachycardia that must be distinguished from ventricular tachycardia (**Chap. 18**). Supraventricular tachyarrhythmia may be divided into physiologic sinus tachycardia and pathologic tachycardia (**Table 17-1**). The prognosis and treatment vary considerably depending on the mechanism and underlying heart disease.

Supraventricular tachycardia can be of brief duration, termed nonsustained, or can be sustained such that an intervention, such as cardioversion or drug administration, is required for termination. Episodes that occur with sudden onset and termination are referred to as paroxysmal. Paroxysmal supraventricular tachycardia (PSVT) refers to a family of tachycardias including AV node reentry, AV reentry using an accessory pathway, and atrial tachycardia.

CLINICAL PRESENTATION

Symptoms of supraventricular arrhythmia vary depending on the rate, duration, associated heart disease, and comorbidities and include palpitations, chest pain, dyspnea, diminished exertional capacity, and occasionally syncope. Rarely, a supraventricular arrhythmia precipitates cardiac arrest in patients with the Wolff-Parkinson-White syndrome or severe heart disease, such as hypertrophic cardiomyopathy.

Diagnosis requires obtaining an electrocardiogram (ECG) at the time of symptoms. For transient arrhythmia, ambulatory ECG recording is warranted (see

Table 18-1). Exercise testing is useful for assessing exercise-related symptoms. Occasionally an invasive electrophysiology study is warranted to provoke the arrhythmia with pacing, confirm the mechanism, and often, perform catheter ablation.

Physiologic sinus tachycardia

The sinus node is comprised of a group of cells dispersed within the superior aspect of the thick ridge of muscle known as the crista terminalis where the posterior smooth atrial wall derived from the sinus venosus meets the trabeculated anterior portion of the right atrium (**Fig. 17-1**). Sinus p waves are characterized by a frontal plane axis directed inferiorly and leftward, with positive p waves in leads II, III, and aVF; a negative p wave in aVR; and an initially positive biphasic p wave in V1. Normal sinus rhythm has a rate of 60–100 beats/min. Sinus tachycardia (>100 beats/min) typically occurs in response to sympathetic stimulation and vagal withdrawal, whereby the rate of spontaneous depolarization of the sinus node increases and the focus of earliest activation within the node typically shifts more leftward and closer to the superior septal aspect of the crista terminalis, thus producing taller p waves in the inferior limb leads when compared to normal sinus rhythm.

Sinus tachycardia is considered physiologic when it is an appropriate response to exercise, stress, or illness. Sinus tachycardia can be difficult to distinguish from focal atrial tachycardia (see below) that originates from a focus near the sinus node. A causative factor (such as exertion) and a gradual increase and decrease in rate favors sinus tachycardia, whereas an abrupt onset and offset favor atrial tachycardia. The distinction can be difficult and occasionally requires extended ECG monitoring or even invasive electrophysiology study. Treatment for physiologic sinus tachycardia is aimed at the underlying condition (**Table 17-2**).

TABLE 17-1

SUPRAVENTRICULAR TACHYCARDIA
I. Physiologic sinus tachycardia Defining feature: normal sinus mechanism precipitated by exertion, stress, concurrent illness (Table 17-2)
II. Pathologic supraventricular tachycardia A. Tachycardia originating from the atrium Defining feature: tachycardia may continue despite beats that fail to conduct to the ventricles, indicating that the AVnode is not participating in the tachycardia circuit 1. Inappropriate sinus tachycardia Defining feature: tachycardia from the normal sinus node area that occurs without an identifiable precipitating factor as a result of dysfunctional autonomic regulation 2. Focal atrial tachycardia Defining feature: Regular atrial tachycardia with defined p wave; may be sustained, nonsustained, paroxysmal, or incessant. Frequent sites of origin occur along the valve annuli of left or right atrium, pulmonary veins, coronary sinus musculature, superior vena cava 3. Atrial flutter – macroreentrant atrial tachycardia Defining feature: organized reentry creates organized atrial activity, commonly seen as sawtooth flutter waves at rates typically faster than 200 beats/min a. Common atrial flutter i. Right atrial reentry parallel to the tricuspid annulus and dependent on conduction through the isthmus between the inferior vena cava and tricuspid annulus 1. Counterclockwise (as viewed from the ventricular aspect) 2. Clockwise b. Atypical atrial flutter i. Usually due to reentry in left or right atrium associated with scars usually from prior surgery or catheter ablation for atrial fibrillation, but may be idiopathic 4. Atrial fibrillation Defining feature: chaotic rapid atrial electrical activity with variable ventricular rate; the most common sustained cardiac arrhythmia in older adults 5. Multifocal atrial tachycardia Defining feature: multiple discrete p waves often seen in patients with pulmonary disease during acute exacerbations of pulmonary insufficiency B. AV nodal reentry tachycardia Defining feature: paroxysmal regular tachycardia with P waves visible at the end of the QRS complex or not visible at all; the most common paroxysmal sustained tachycardia in healthy young adults; more common in women C. Tachycardias associated with accessory atrioventricular pathways a. Orthodromic AVreentry tachycardia Defining feature: paroxysmal sustained tachycardia similar to AVnodal reentry; during sinus rhythm, evidence of ventricular preexcitation may be present (Wolf -Parkinson-White syndrome) or absent (concealed accessory pathway) b. Preexcited tachycardia Defining feature: wide QRS tachycardia with QRS morphology similar to VT 1. Antidromic AVreentry – regular paroxysmal tachycardia 2. Atrial fibrillation with preexcitation–irregular wide complex, or intermittently wide complex tachycardia, some with dangerously rapid rates faster than 250/min 3. Atrial tachycardia or flutter with preexcitation

Abbreviations: AV, **atrioventricular**; VT, ventricular tachycardia.

Nonphysiologic sinus tachycardia

Inappropriate sinus tachycardia is an uncommon condition in which the sinus rate increases spontaneously at rest or out of proportion to physiologic stress or exertion. Affected individuals are often women in the third or fourth decade of life. Fatigue, dizziness, and even

syncope may accompany palpitations, which can be disabling. Additional symptoms of chest pain, headaches, and gastrointestinal upset are common. It must be distinguished from appropriate sinus tachycardia and from focal atrial tachycardia, as discussed above. Misdiagnosis of physiologic sinus tachycardia with an anxiety

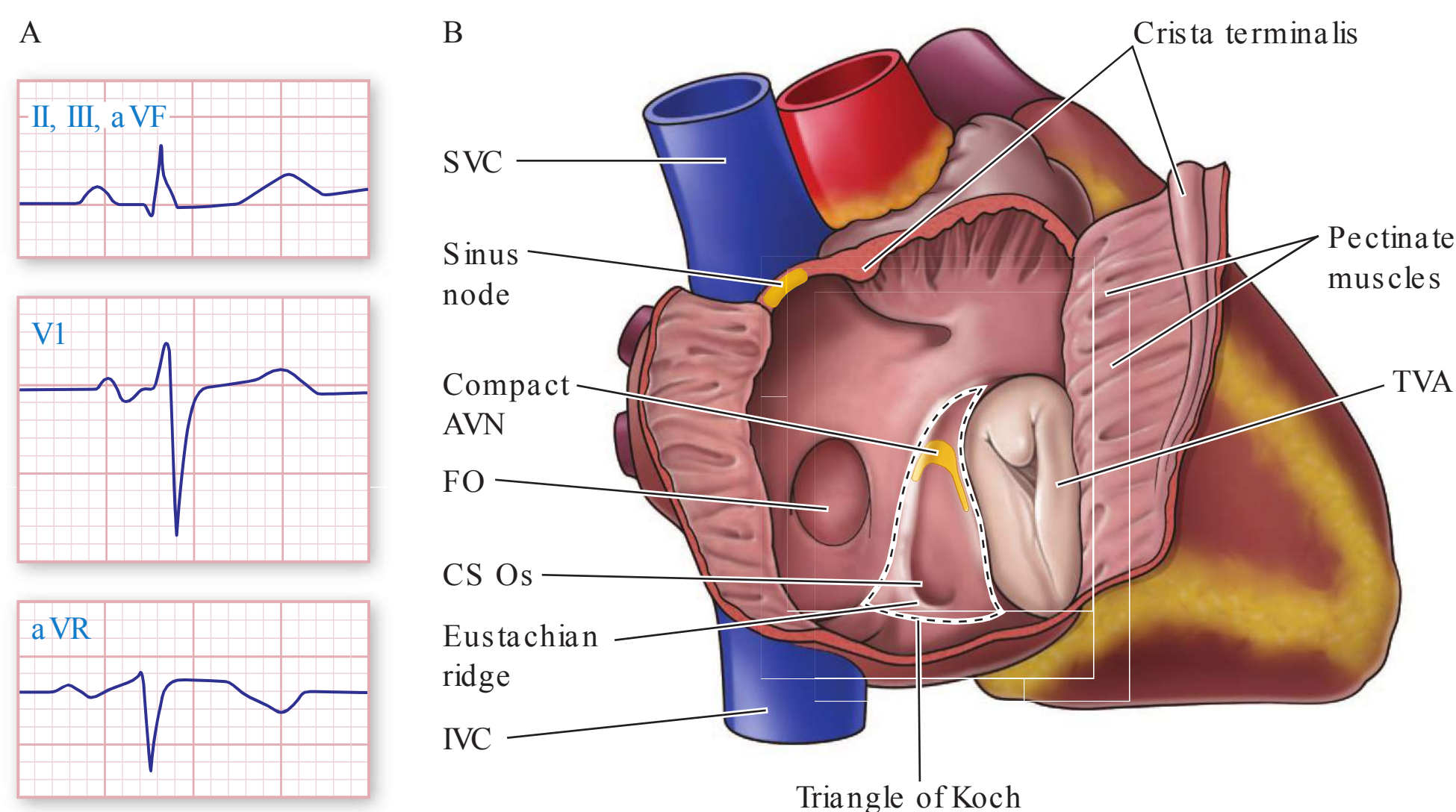


FIGURE 17-1

Right atrial anatomy pertinent to normal sinus rhythm and supraventricular tachycardia. A. Typical P-wave morphology during normal sinus rhythm based on standard 12-lead electrocardiogram. There is a positive P wave in leads II, III, and aVF; biphasic, initially positive P wave in V_1 ; and negative P wave in

aVR. B. Right atrial anatomy seen from a right lateral perspective with the lateral wall opened to view the septum. AVN, atrioventricular node; CS Os, coronary sinus ostium; FO, fossa ovalis; IVC, inferior vena cava; SVC, superior vena cava; TVA, tricuspid valve annulus.

disorder is common. Therapy is often ineffective or poorly tolerated. Careful titration of beta blockers and/or calcium channel blockers may reduce symptoms. Clonidine and serotonin reuptake inhibitors have also been used. Ivabradine, a drug that blocks the I_f current causing sinus node depolarization, is promising but is not approved for use in the United States. Catheter ablation of the sinus node has been used, but long-term control of symptoms is usually poor, and it often leaves young individuals with a permanent pacemaker.

When symptomatic sinus tachycardia occurs with postural hypotension, the syndrome is called postural orthostatic tachycardia syndrome (POTS). Symptoms are often similar to those in patients with inappropriate sinus tachycardia. POTS is sometimes due to autonomic dysfunction following a viral illness and may resolve spontaneously over 3–12 months. Volume expansion

with salt supplementation, oral fludrocortisone, compression stockings, and the α -agonist midodrine, often in combination, can be helpful. Exercise training has also been purported to improve symptoms.

Focal atrial tachycardia

Focal atrial tachycardia (AT) can be due to abnormal automaticity, triggered automaticity, or a small reentry circuit confined to the atrium or atrial tissue extending into a pulmonary vein, the coronary sinus, or vena cava. It can be sustained, nonsustained, paroxysmal, or incessant. Focal AT accounts for approximately 10% of PSVT referred for catheter ablation. Nonsustained AT is commonly observed on 24-h ambulatory ECG recordings, and the prevalence increases with age. Tachycardia can occur in the absence of structural heart disease or can be associated with any form of heart disease that affects the atrium. Sympathetic stimulation is a promoting factor such that AT can be a sign of underlying illness. AT with AV block can occur in digitalis toxicity. Symptoms are similar to other supraventricular tachycardias (SVTs). Incessant AT can cause tachycardia-induced cardiomyopathy.

AT typically presents as an SVT either with 1:1 AV conduction or with AV block that can be Wenckebach type conduction or fixed (e.g., 2:1 or 3:1) block. Because it is not dependent on AV nodal conduction, AT will not terminate with AV block, and the atrial rate will not be affected, which distinguishes AT from most AV

TABLE 17-2

COMMON CAUSES OF PHYSIOLOGIC SINUS TACHYCARDIA

1. Exercise
2. Acute illness with fever, infection, pain
3. Hypovolemia, anemia
4. Hyperthyroidism
5. Pulmonary insufficiency
6. Drugs that have sympathomimetic, vagolytic, or vasodilator properties, e.g., albuterol, theophylline, tricyclic antidepressants, nifedipine, hydralazine
7. Pheochromocytoma

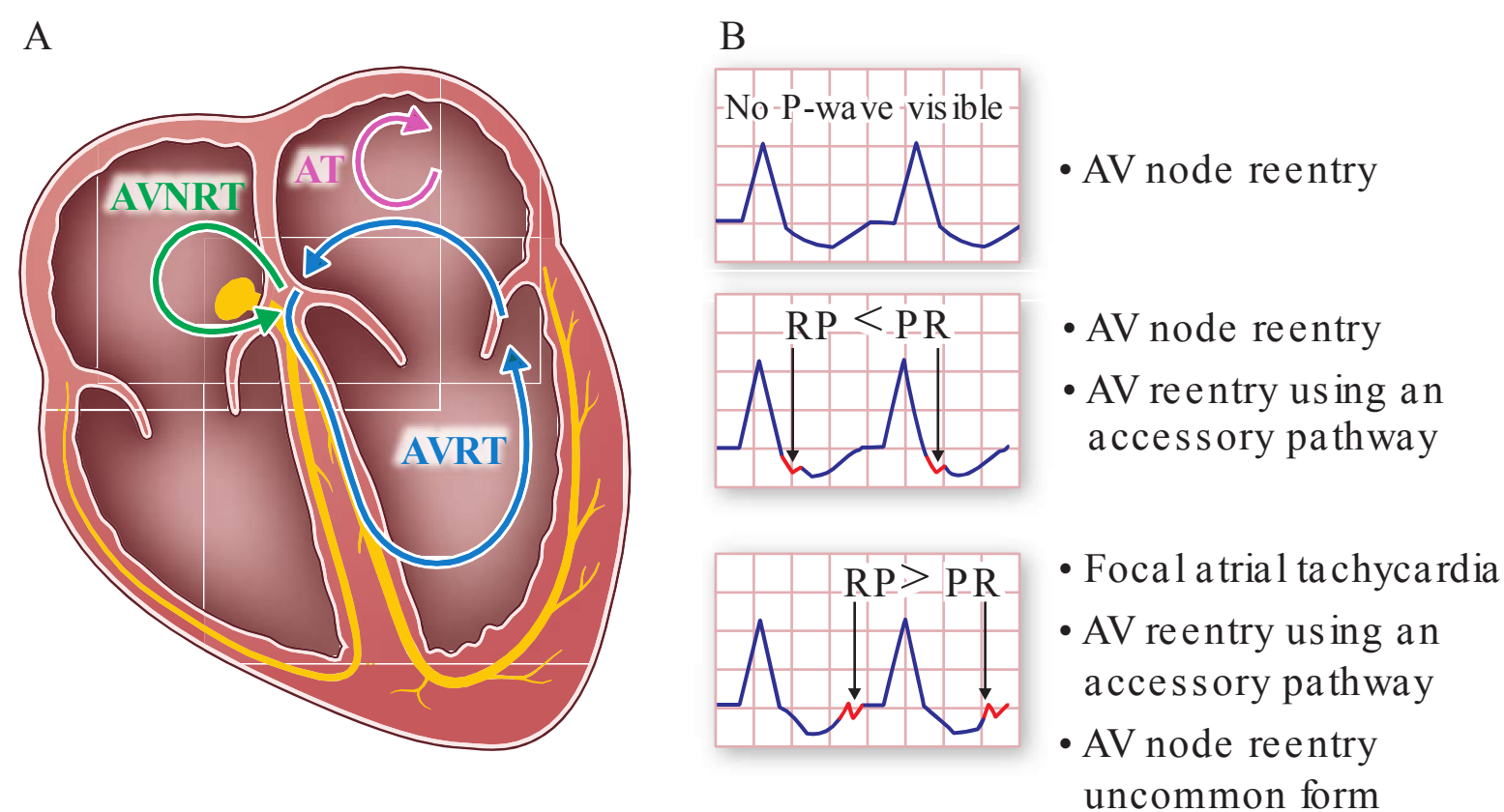


FIGURE 17-2

Common mechanisms underlying paroxysmal supraventricular tachycardia along with typical R-P relationships.

A. Schematic showing a four-chamber view of the heart with atrioventricular node in green and an accessory pathway between the left atrium and left ventricle in blue. Atrial tachycardia (AT; red circuit) is confined completely to atrial tissue. Atrioventricular nodal reentry tachycardia (AVNRT; blue circuit) uses

atrioventricular (AV) nodal and perinodal atrial tissue. Atrioventricular reentry tachycardia (AVRT; black circuit) uses atrial and ventricular tissue, accessory pathway, AV node, and specialized conduction fibers (His-Purkinje) as part of the reentry circuit. B. Typical relation of the p wave to QRS, commonly described as the R-P to P-R relationships for the different tachycardia mechanisms.

nodal-dependent SVTs, such as AV nodal reentry and AV reentry using an accessory pathway (see below). An accelerated warm-up phase after initiation or cool-down phase prior to termination also favors AT rather than AV nodal-dependent SVT. P waves are often discrete, with an intervening isoelectric segment, in contrast to atrial flutter and macroreentrant AT (see below). When 1:1 conduction to the ventricles is present, the arrhythmia can resemble sinus tachycardia typically with a P-R interval shorter than the R-P interval (**Fig. 17-2**). It can be distinguished from sinus tachycardia by the p-wave morphology, which usually differs from sinus p waves depending on the location of the focus. Focal AT tends to originate in areas of complex atrial anatomy, such as the crista terminalis, valve annuli, atrial septum, and atrial muscle extending along cardiac thoracic veins (superior vena cava, coronary sinus, and pulmonary veins) (**Fig. 17-3**), and the location can often be estimated by the P-wave morphology. AT from the right atrium has a positive P-wave morphology in lead I and biphasic P-wave morphology in lead V₁. AT from the atrial septum will frequently have a narrower P-wave duration than sinus rhythm. AT from the left atrium will usually have a monophasic, positive P wave in lead V₁. AT that originates from superior atrial locations, such as the superior vena cava or superior pulmonary veins, will be positive in the inferior limb leads II, III, and aVF, whereas AT from a more inferior location, such as the ostium of the coronary sinus, will inscribe negative P waves in these same leads. When the focus is in the superior aspect of the crista terminalis, close to the sinus node, however, the p wave will resemble that of sinus tachycardia. Abrupt onset and offset then favor AT

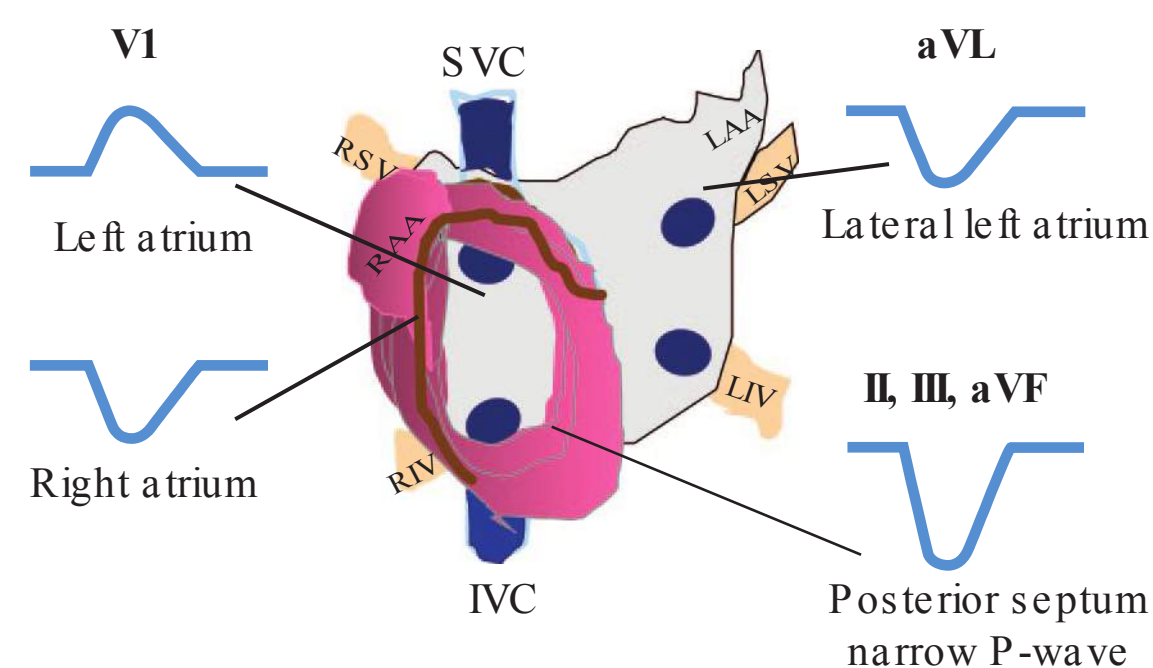


FIGURE 17-3

Location of focal atrial tachycardia focus estimated by P-wave morphology.

LAA, left atrial appendage; LIV, left inferior pulmonary vein; LSV, left superior pulmonary vein; RAA, right atrial appendage; RIV, right inferior pulmonary vein; RSV, right superior pulmonary vein; SVC, superior vena cava.

rather than sinus tachycardia. Depending on the atrial rate, the P wave may fall on top of the t wave or, during 2:1 conduction, may fall coincident with the QRS. Maneuvers that increase AV block, such as carotid sinus massage, Valsalva maneuver, or administration of AV nodal-blocking agents, such as adenosine, are useful to create AV block that will expose the p wave (**Fig. 17-4**).

Acute management of sudden-onset, sustained AT is the same as for PSVT (see below), but the response to pharmacologic therapy is variable, likely depending on the mechanism. For AT due to reentry, administration of adenosine or vagal maneuvers may transiently increase AV block without terminating tachycardia. Some ATs terminate with a sufficient dose of adenosine, consistent with triggered activity as the mechanism.

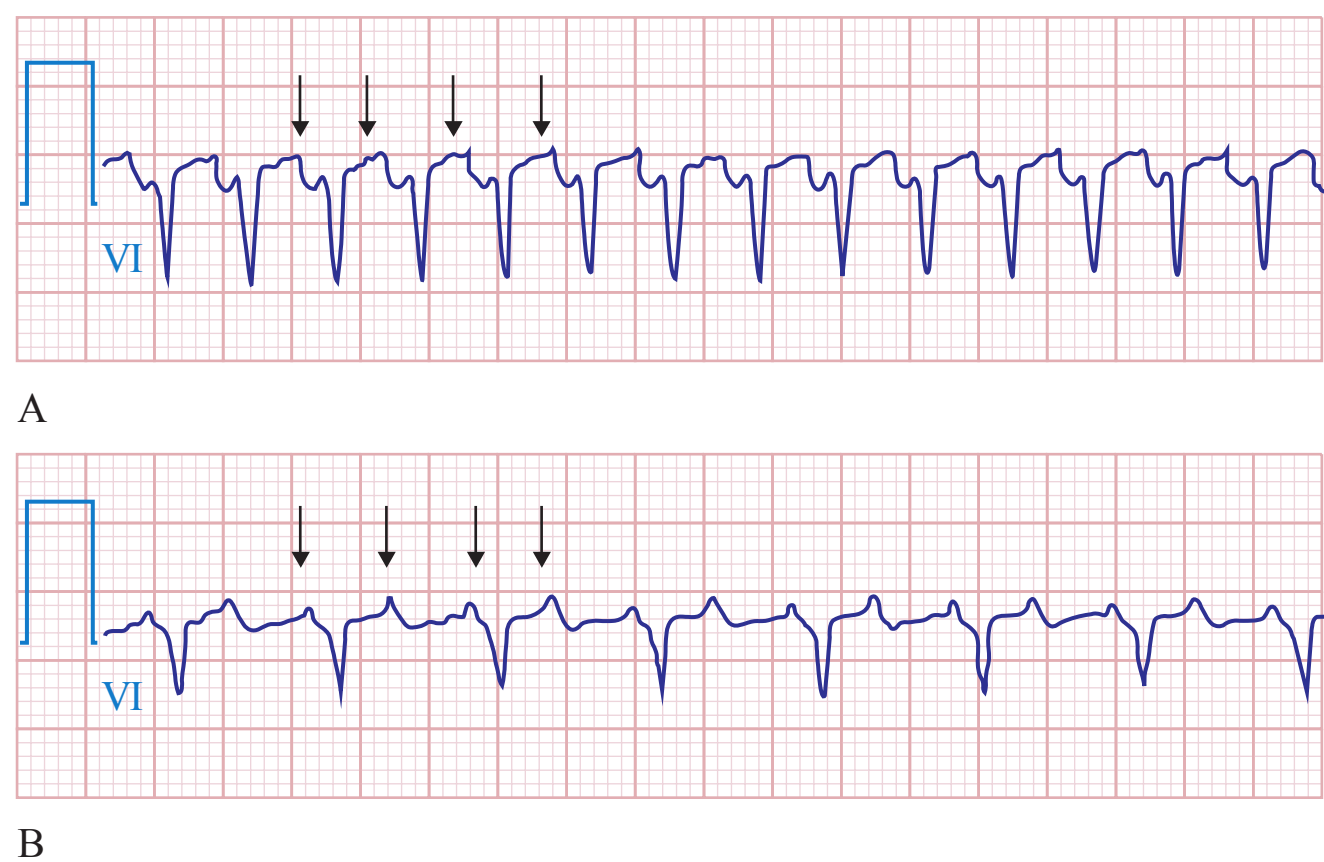


FIGURE 17-4

Atrial tachycardia (AT) with 1:1 and 2:1 atrioventricular (AV) conduction. Arrows indicate p waves. A. AT with 1:1 AV relationship and R-P > P-R. B. Same AT with 2:1 AV relationship after AV nodal-blocking agent administered. (Adapted from F Marchlinski: The tachyarrhythmias. In Longo DL et al [eds]: *Harrison's Principles of Internal Medicine*, 18th ed. New York, McGraw-Hill, 2012, pp 1878–1900.)

Cardioversion can be effective in some, but fails in others, suggesting automaticity as the mechanism. Beta blockers and calcium channel blockers may slow the ventricular rate by increasing AV block, which can

improve tolerance of the arrhythmias. Potential precipitating factors and intercurrent illness should be sought and corrected. Underlying heart disease should be considered and excluded.

For patients with recurrent episodes, beta blockers, the calcium channel blockers diltiazem or verapamil, and the antiarrhythmic drugs flecainide, propafenone, disopyramide, sotalol, and amiodarone can be effective, but potential toxicities and adverse effects often warrant avoiding these agents (Tables 17-3, 17-4, and 17-5). Catheter ablation targeting the AT focus is effective in more than 80% of patients and is recommended for recurrent symptomatic AT when drugs fail or are not desired or for incessant AT causing tachycardia-induced cardiomyopathy.

Atrioventricular nodal reentry tachycardia

AV nodal reentry tachycardia (AVNRT) is the most common form of PSVT, representing approximately 60% of cases referred for catheter ablation. It most commonly manifests in the second to fourth decades of life, often in women. It is often well tolerated, but rapid tachycardia, particularly in the elderly, may cause angina, pulmonary edema, hypotension, or syncope. It is not usually associated with structural heart disease.

TABLE 17-3

COMMONLY USED ANTIARRHYTHMIC AGENTS—INTRAVENOUS DOSE RANGE/PRIMARY INDICATION				
DRUG	LOADING	MAINTENANCE	PRIMARY INDICATION	CLASS ^a
Adenosine	6–18 mg (rapid bolus)	N/A	Terminate reentrant SVT involving AV node	—
Amiodarone	15 mg/min for 10 min, 1 mg/min for 6 h	0.5–1 mg/min	AF, AFL, SVT, VT/VF	III
Digoxin	0.25 mg q2h until 1 mg total	0.125–0.25 mg/d	AF/AFL rate control	—
Diltiazem	0.25 mg/kg over 3–5 min (max 20 mg)	5–15 mg/h	SVT, AF/AFL rate control	IV
Esmolol	500 µg/kg over 1 min	50 µg/kg per min	AF/AFL rate control	II
Ibutilide	1 mg over 10 min if over 60 kg	N/A	Terminate AF/AFL	III
Lidocaine	1–3 mg/kg at 20–50 mg/min	1–4 mg/min	VT	IB
Metoprolol	5 mg over 3–5 min × 3 doses	1.25–5 mg q6h	SVT, AF rate control; exercise-induced VT; long QT	II
Procainamide	15 mg/kg over 60 min	1–4 mg/min	Convert/prevent AF/VT	IA
Quinidine	6–10 mg/kg at 0.3–0.5 mg/kg per min	N/A	Convert/prevent AF/VT	IA
Verapamil	5–10 mg over 3–5 min	2.5–10 mg/h	SVT, AF rate control	IV

^aClassification of antiarrhythmic drugs: class I—agents that primarily block inward sodium current; class IA agents also prolong action potential duration; class II—antisympathetic agents; class III—agents that primarily prolong action potential duration; class IV—calcium channel-blocking agents. Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AV, atrioventricular; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 17-4

COMMONLY USED ANTIARRHYTHMIC AGENTS: CHRONIC ORAL DOSING/PRIMARY INDICATIONS					
DRUG	DOSING ORAL, MG, MAINTENANCE	HALF-LIFE, H	PRIMARY ROUTE(S) OF METABOLISM/ ELIMINATION	MOST COMMON INDICATION	CLASS ^a
Acebutolol	200–400 q12h	6–7	Renal/hepatic	AF rate control/SVT Long QT/RVOTVT	II
Amiodarone	100–400 qd	40–55 d	Hepatic	AF/VT prevention	IIIb
Atenolol	25–100 per d	6–9	Renal	AF rate control/SVT Long QT/RVOTVT	II
Digoxin	0.125–0.25 qd	38–48	Renal	AF rate control	—
Diltiazem	30–60 q6h	3–4.5	Hepatic	AF rate control/SVT	IV
Disopyramide	100–300 q6–8h	4–10	Renal 50%/hepatic	AF/SVT prevention	Ia
Dofetilide	0.125–0.5 q12h	10	Renal	AF prevention	III
Dronedarone	400 q12h	13–19	Hepatic	AF prevention	IIIb
Flecainide	50–200 q12h	7–22	Hepatic 75%/renal	AF/SVT/VT prevention	Ic
Metoprolol	25–100 q6h	3–8	Hepatic	AF rate control/SVT Long QT/RVOTVT	II
Mexiletine	150–300 q8–12h	10–14	Hepatic	VT prevention	Ib
Nadolol	40–240 per d	10–24	Renal	Same as metoprolol	II
Propafenone	150–300 q8h	2–8	Hepatic	AF/SVT/VT prevention	Ic
Quinidine	300–600 q6h	6–8	Hepatic 75%/renal	AF/SVT/VT prevention	Ia
Sotalol	80–160 q12h	12	Renal	AF/VT prevention	III
Verapamil	80–120 q6–8h	4.5–12	Hepatic/renal	AF rate control/ RVOTVT Idiopathic LVVT	IV

^aClassification of antiarrhythmic drugs: class I—agents that primarily block inward sodium current; class II—antisympathetic agents; class III—agents that primarily prolong action potential duration; class IV—calcium channel-blocking agents.
^bAmiodarone and dronedarone both are grouped in class III, but both also have class I, II, and IV properties.
Abbreviations: AF, atrial fibrillation; LV, left ventricular; RVOT, right ventricular outflow tract; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

The mechanism is reentry involving the AV node and likely the perinodal atrium, made possible by the existence of multiple pathways for conduction from the atrium into the AV node (Fig. 17-5). In the most common form, a slowly conducting AV nodal pathway extends from the compact AV node near the bundle of His, inferiorly along the tricuspid annulus, adjacent to the coronary sinus os. The reentry wavefront propagates up this slow pathway to the compact AV node and then exits from the fast pathway at the top of the AV node. The path back to the slow pathway to complete the circuit is not defined. The conduction time from the compact AV node region to the atrium is similar to that from the compact node to the His bundle and ventricles, such that atrial activation occurs at about the same time as ventricular activation. The p wave is therefore inscribed during, slightly before, or slightly after the

QRS and can be difficult to discern. Often the P wave is seen at the end of the QRS complex as a pseudo-r' in lead V₁ and pseudo-S waves in leads II, III, and aVF (Fig. 17-5A). The rate can vary with sympathetic tone. Simultaneous atrial and ventricular contraction results in atrial contraction against a closed tricuspid valve that produces cannon waves visible in the jugular venous pulse and that the patient often perceives as a fluttering sensation in the neck. Elevated venous pressures may also lead to release of natriuretic peptides that cause posttachycardia diuresis. Less frequently, the AV nodal reentry circuit revolves in the opposite direction and gives rise to a tachycardia with an R-P interval longer than the P-R interval, similar to AT. The p wave will have the morphology noted above, and in contrast to ATs, maneuvers or medications that produce AV block terminate the arrhythmia.

TABLE 17-5

COMMON AND PROARRHYTHMIC TOXICITIES OF ANTIARRHYTHMIC AGENTS		
DRUG	POTENTIAL PROARRHYTHMIC TOXICITIES	COMMON TOXICITIES
Amiodarone	Sinus bradycardia, AVblock, increase in defibrillation threshold. Rare: long QT and torsades des pointes, incessant slow VT in heart disease	Tremor, peripheral neuropathy, pulmonary fibrosis or inflammation, hypo- and hyperthyroidism, hepatitis, photosensitivity
Adenosine	Transient profound pauses, atrial fibrillation	Cough, flushing, chest pain, anxiety
Digoxin	AVblock, fascicular tachycardia, accelerated junctional rhythm, atrial tachycardia with AVblock	Anorexia, nausea, vomiting, visual changes
Disopyramide	Long QT and torsades des pointes, 1:1 ventricular response to atrial flutter	Anticholinergic effects, acute urinary retention (males), negative inotropy
Dofetilide	Long QT and torsades des pointes	Nausea
Dronedarone	Bradyarrhythmias and AVblock, long QT and torsades des pointes (rare)	Gastrointestinal intolerance, exacerbation of heart failure
Flecainide	1:1 Ventricular response to atrial flutter; increased risk of ventricular tachycardias in patients with structural heart disease; sinus bradycardia	Dizziness, nausea, headache, decreased myocardial contractility
Ibutilide	Long QT and torsades des pointes	Nausea
Lidocaine	Slow VT in some patients with structural heart disease	Dizziness, confusion, delirium, seizures, coma
Mexiletine	Slow VT in patients with structural heart disease	Ataxia, tremor, gait disturbances, rash, nausea
Procainamide	Long QT and torsades des pointes, accelerated ventricular rate in AF or flutter	Lupus erythematosus–like syndrome (more common in slow acetylators), anorexia, nausea, neutropenia
Propafenone	1:1 Ventricular response to atrial flutter; increased risk ventricular tachycardias in patients with structural heart disease; sinus bradycardia	Taste disturbance, dyspepsia, nausea, vomiting
Quinidine	Long QT and torsades des pointes, accelerated ventricular rate in AF or flutter	Diarrhea, nausea, vomiting, cinchonism, thrombocytopenia
Sotalol	Long QT and torsades des pointes	Hypotension, bronchospasm from β -blocking effect

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; VT, ventricular tachycardia.

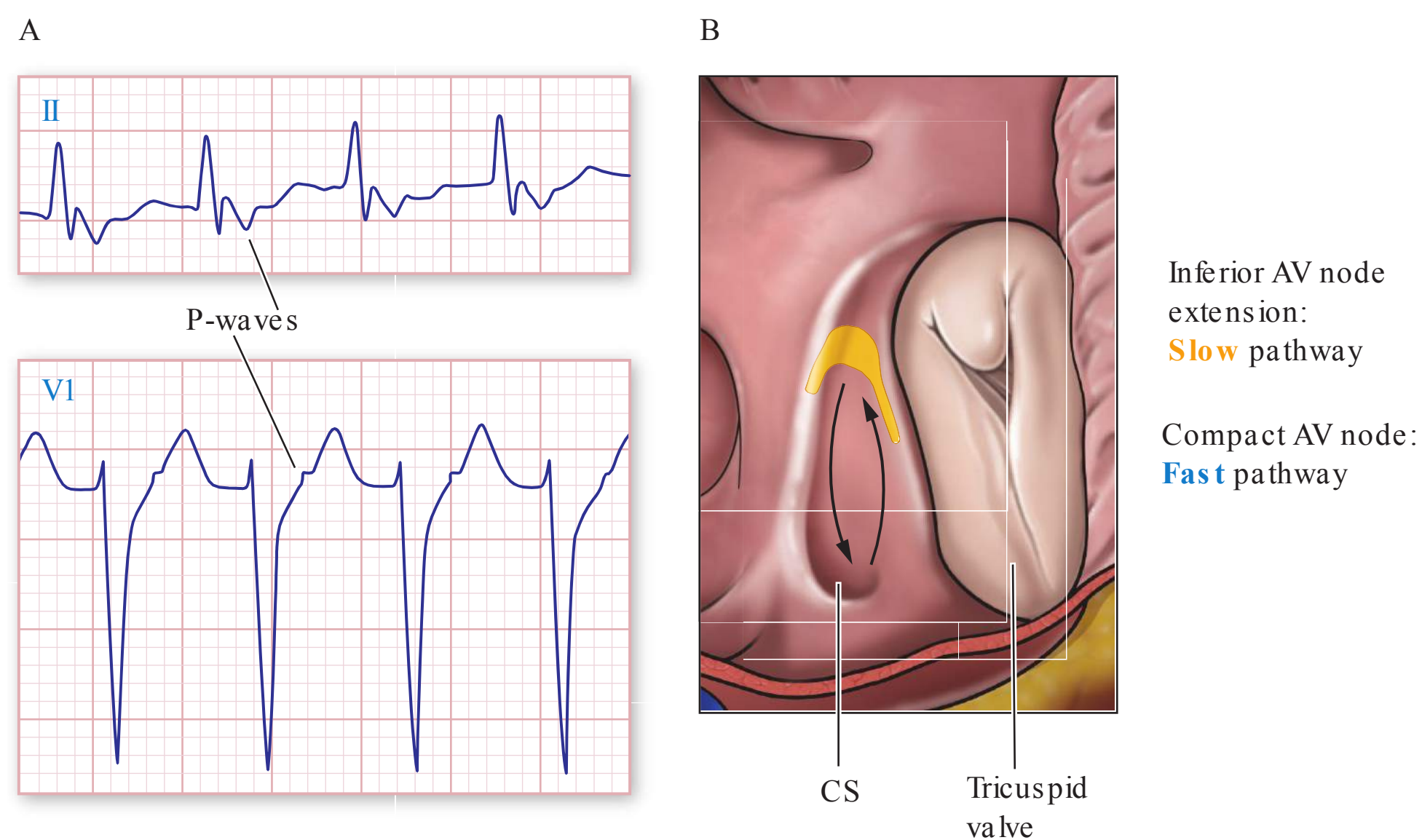


FIGURE 17-5

Atrioventricular (AV) node reentry. A. Leads II and V₁ are shown. P waves are visible at the end of the QRS complex and are negative in lead II, and may give the impression of S waves in the inferior limb leads II, III, and aVF and an R' in lead V₁. B. Stylized

version of the AV nodal reentry circuit within the triangle of Koch (Fig. 17-1) that involves AV node and its extensions along with perinodal atrial tissue.

Acute treatment is the same as for PSVT (discussed below). Whether ongoing therapy is warranted depends on the severity of symptoms and frequency of episodes. Reassurance and instruction as to performance of the Valsalva maneuver to terminate episodes are sufficient for many patients. Administration of an oral beta blocker, verapamil, or diltiazem at the onset of an episode has been used to facilitate termination. Chronic therapy with these medications or flecainide is an option if prophylactic therapy is needed. Catheter ablation of the slow AV nodal pathway is recommended for patients with recurrent or severe episodes or when drug therapy is ineffective, not tolerated, or not desired by the patient. Catheter ablation is curative in over 95% of patients. The major risk is heart block requiring permanent pacemaker implantation, which occurs in less than 1% of patients.

Junctional tachycardia

Junctional ectopic tachycardia (JET) is due to automaticity within the AV node. It is rare in adults and more frequently encountered as an incessant tachycardia in children, often in the perioperative period of surgery for congenital heart disease. It presents as a narrow QRS tachycardia, often with ventriculoatrial (VA) block, such that AV dissociation is present. JET can occur as a manifestation of increased adrenergic tone and may be seen after administration of isoproterenol. It may also occur for a short period of time after ablation for AVNRT.

Accelerated junctional rhythm is a junctional automatic rhythm between 50 and 100 beats/min. Initiation may occur with gradual acceleration in rate, suggesting an automatic focus, or after a premature ventricular contraction, suggesting a focus of triggered automaticity. VA conduction is usually present, with p-wave morphology and timing such that it resembles slow AVNRT.

ACCESSORY PATHWAYS AND THE WOLFF-PARKINSON-WHITE SYNDROME

Accessory pathways (APs) occur in 1 in 1500–2000 people and are associated with a variety of arrhythmias including narrow-complex PSVT, wide-complex tachycardias, and, rarely, sudden death. Most patients have structurally normal hearts, but APs are associated with Ebstein's anomaly of the tricuspid valve and forms of hypertrophic cardiomyopathy including PRKAG2 mutations, Danon's disease, and Fabry's disease.

APs are abnormal connections that allow conduction between the atrium and ventricles across the AV ring (Fig. 17-6). They are present from birth and are due to failure of complete partitioning of atrium and ventricle by the fibrous AV rings. They occur across

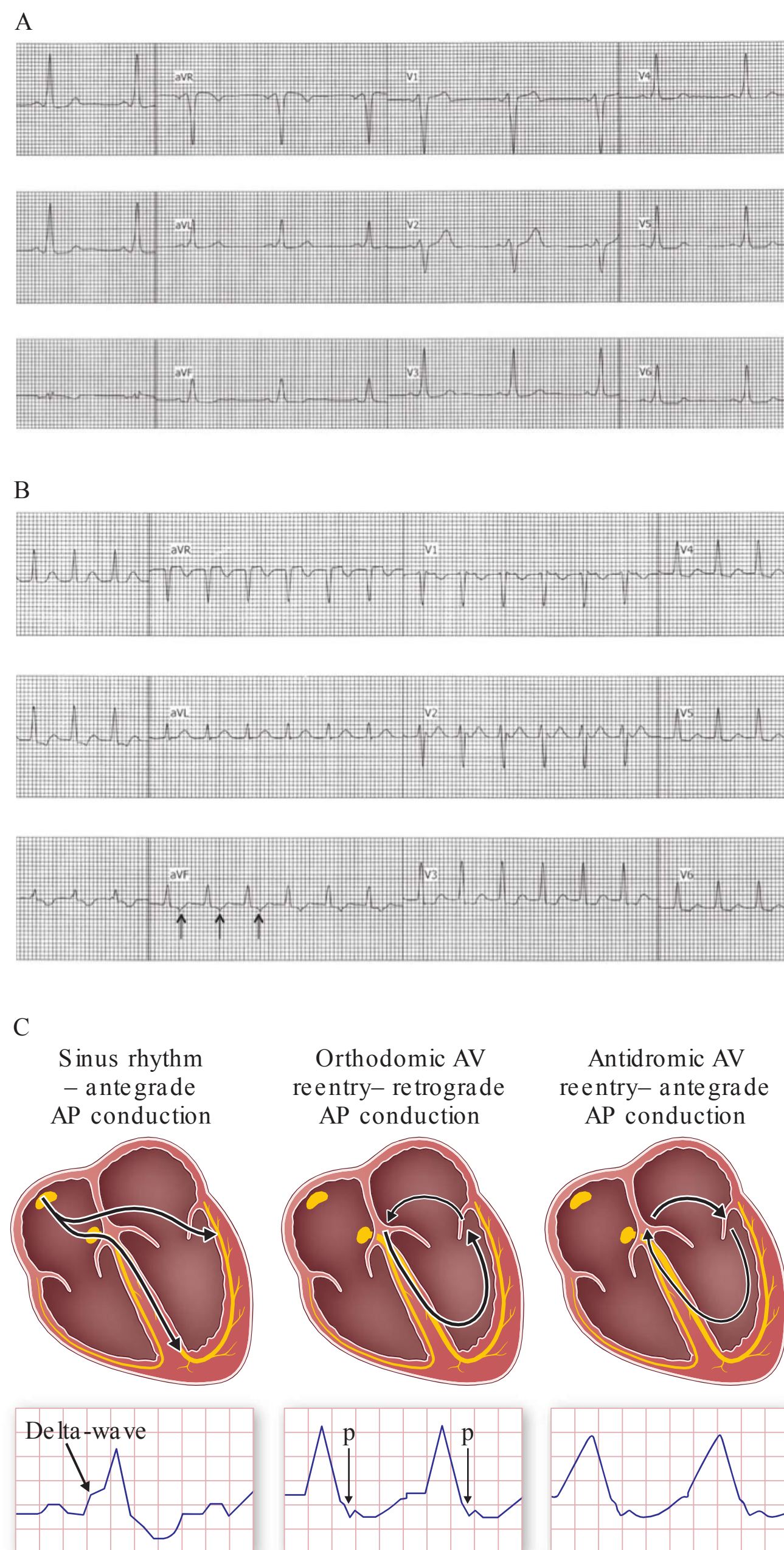


FIGURE 17-6

Wolff-Parkinson-White (WPW) syndrome. A. A 12-lead electrocardiogram in sinus rhythm (SR) of a patient with WPW demonstrating short P-R interval, delta waves, and widened QRS complex. This patient had an anteroseptal location of the AP. B. Orthodromic AV reentry in a patient with WPW syndrome using a posteroseptal AP. Note the P waves in the ST segment (arrows) seen in lead III and normal appearance of QRS complex. C. Three most common rhythms associated with WPW syndrome: sinus rhythm demonstrating antegrade conduction over the AP and AV node; orthodromic AVRT using retrograde conduction over the AP and antegrade conduction over the AV node; and antidromic AVRT using retrograde conduction over the AV node and antegrade conduction over the AP. AP, accessory pathway; AV, atrioventricular; AVRT, atrioventricular reentry tachycardia; WPW, Wolf-Parkinson-White.

either an AV valve annulus or the septum, most frequently between the left atrium and free wall of the left ventricle, followed by posteroseptal, right free wall, and anteroseptal locations. If the AP conducts from atrium to ventricle (antegrade) with a shorter conduction time than the AV node and His bundle, then the ventricles are preexcited during sinus rhythm, and the ECG shows a short P-R interval (<0.12 s), slurred initial portion of the QRS (delta wave), and prolonged QRS duration produced by slow conduction through direct activation of ventricular myocardium over the AP (Fig. 17-6A). The morphology of the QRS and delta wave is determined by the AP location (Fig. 17-7) and the degree of fusion between the excitation wavefronts from conduction over the AV node and conduction over the AP. Right-sided pathways preexcite the right ventricle, producing a left bundle branch block-like configuration in lead V_1 , and often show marked preexcitation because of relatively close proximity of the AP to the sinus node (Fig. 17-7). Left-sided pathways preexcite the left ventricle and may produce a right bundle branch block-like configuration in lead V_1 and a negative delta wave in aVL, indicating initial

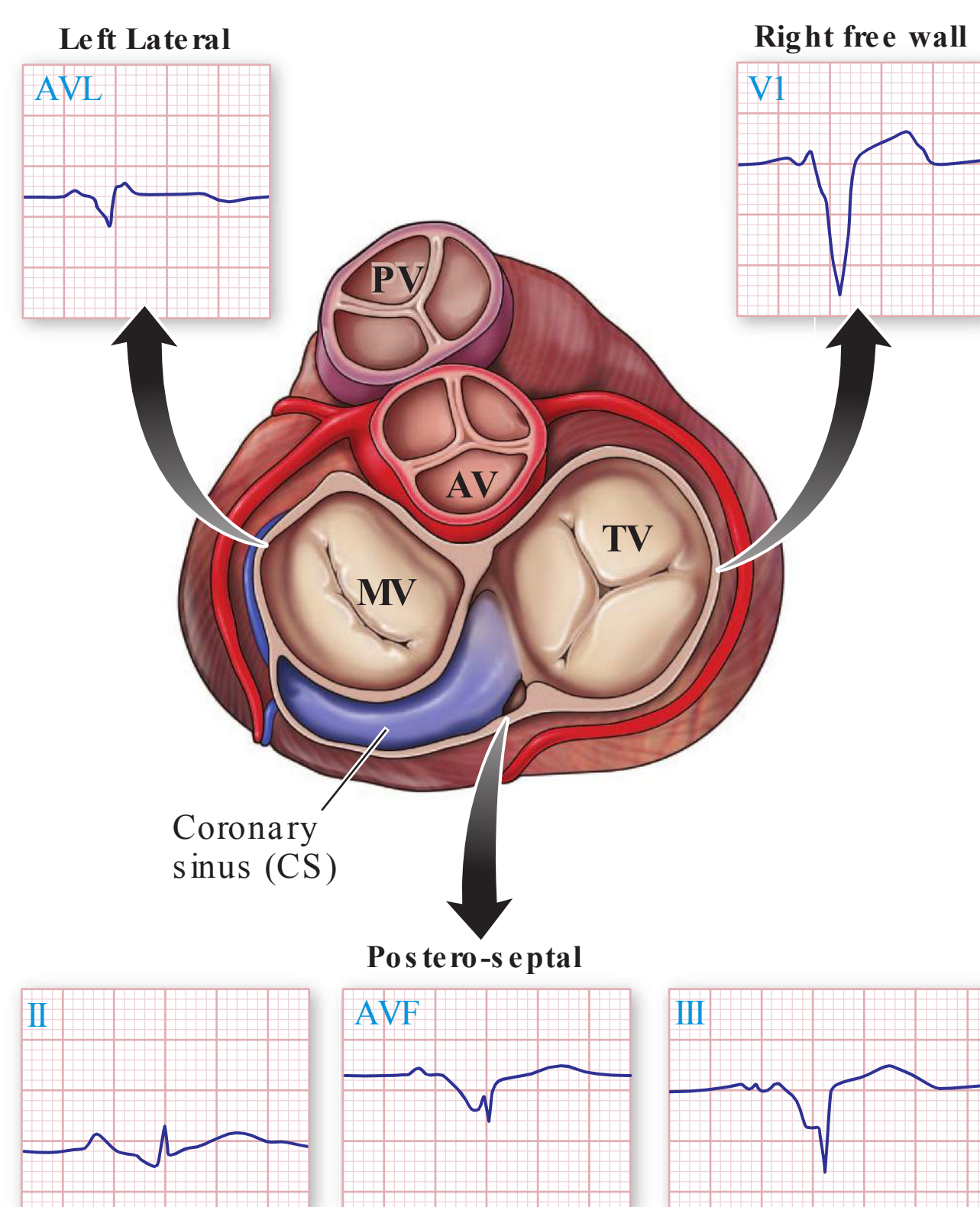


FIGURE 17-7

Potential locations for accessory pathways in patients with Wolff-Parkinson-White Syndrome and typical QRS appearance of delta waves that can mimic underlying structural heart disease such as myocardial infarction or bundle branch block. AV, aortic valve; MV, mitral valve; PV, pulmonary valve; TV, tricuspid valve.

depolarization of the lateral portion of the left ventricle that can mimic q waves of lateral wall infarction (Fig. 17-7). Preexcitation due to an AP at the diaphragmatic surface of the heart, typically in the paraseptal region, produces delta waves that are negative in leads III and aVF, mimicking the q waves of inferior wall infarction (Fig. 17-7). Preexcitation can be intermittent and disappear during exercise as conduction over the AV node accelerates and takes over ventricular activation completely.

Wolff-Parkinson-White (WPW) syndrome is defined as a preexcited QRS during sinus rhythm and episodes of PSVT. There are a number of variations of APs, which may not cause preexcitation and/or arrhythmias. Concealed APs allow only retrograde conduction, from ventricle to atrium, so no preexcitation is present during sinus rhythm, but SVT can occur. Fasciculoventricular connections between the His bundle and ventricular septum produce preexcitation but do not cause arrhythmia, nor do fibers such as atrio-Hisian connections, probably because the circuit is too short to promote reentry. Atriofascicular pathways, also known as Mahaim fibers, probably represent a duplicate AV node and His-Purkinje system that connect the right atrium to fascicles of the right bundle branch and conduct slowly only in the anterograde direction.

AV reentry tachycardia

The most common tachycardia caused by an AP is the PSVT designated orthodromic AV reentry. The circulating reentry wavefront propagates from the atrium anterogradely over the AV node and His-Purkinje system to the ventricles and then reenters the atria via retrograde conduction over the AP (Fig. 17-6B). The QRS is narrow or may have typical right or left bundle branch block, but without preexcitation during tachycardia. Because excitation through the normal AV conduction system and AP are necessary, AV or VA block results in tachycardia termination. During sinus rhythm, preexcitation is seen if the pathway also allows anterograde conduction (Fig. 17-6A). Most commonly, during tachycardia the R-P interval is shorter than the P-R interval and can resemble AVNRT (Fig. 17-1). Unlike typical AVNRT, P-wave timing is never simultaneous with a narrow QRS complex because the ventricles must be activated before the reentry wavefront reaches the AP and conducts back to the atrium. The morphology of the P wave is determined by the pathway location, but can be difficult to assess because it is usually inscribed during the ST segment. The p wave in posteroseptal APs is negative in leads II, III, and aVF, similar to that of AV nodal reentry, but P-wave morphology differs from AV nodal reentry for pathways in other locations (Fig. 17-7).

Occasionally, an AP conducts extremely slowly in the retrograde direction, which results in tachycardia with a long R-P interval, similar to most ATs. These pathways are usually located in the septal region and have negative p waves in leads II, III, and aVF. Slow conduction facilitates reentry, often leading to nearly incessant tachycardia, known as paroxysmal junctional reciprocating tachycardia (PJRT). Tachycardia-induced cardiomyopathy can occur. Without an invasive electrophysiology study, it may be difficult to distinguish this form of orthodromic AV reentry from atypical AV nodal reentry or AT.

Preexcited tachycardias

Preexcited tachycardia occurs when the ventricles are activated by antegrade conduction over the AP (Fig. 17-6C). The most common is antidromic AV reentry in which activation propagates from atrium to ventricle via the AP and then conducts retrogradely to the atria via the His-Purkinje system and the AV node (or rarely a second AP). The wide QRS complex is produced entirely via ventricular excitation over the AP because there is no contribution of ventricular activation over more rapidly conducting specialized His-Purkinje fibers. This tachycardia is

often indistinguishable from monomorphic ventricular tachycardia. The presence of preexcitation in sinus rhythm suggests the diagnosis.

Preexcited tachycardia also occurs if an AP allows antegrade conduction to the ventricles during AT, atrial flutter, atrial fibrillation (Fig. 17-8), or AV nodal reentry. Atrial fibrillation and atrial flutter are potentially life threatening if the AP allows very rapid repetitive conduction. Approximately 25% of APs causing preexcitation allow minimum R-to-R intervals of less than 250 ms during atrial fibrillation are therefore associated with a risk of inducing ventricular fibrillation and sudden death. Preexcited atrial fibrillation presents as a wide-complex, very irregular rhythm. During atrial fibrillation, the ventricular rate is determined by the conduction properties of the AP and AV node. The QRS complex can appear quite bizarre and change on a beat-to-beat basis due to the variability in the degree of fusion from activation over the AV node and AP, or all beats may be due to conduction over the AP (Fig. 17-8). Ventricular activation from the Purkinje system may depolarize the ventricular end of the AP and prevent 1:1 atrial wavefront conduction over the AP. Slowing AV nodal conduction can thereby facilitate AP conduction and dangerously accelerate the ventricular rate. Administration of AV nodal-blocking agents including

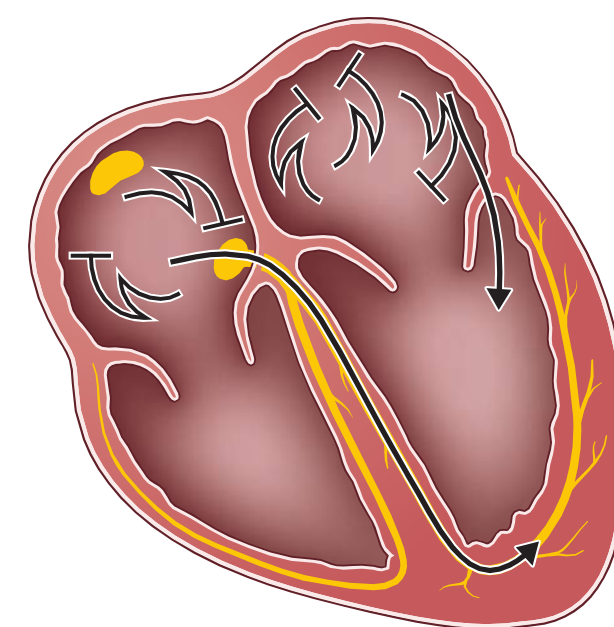
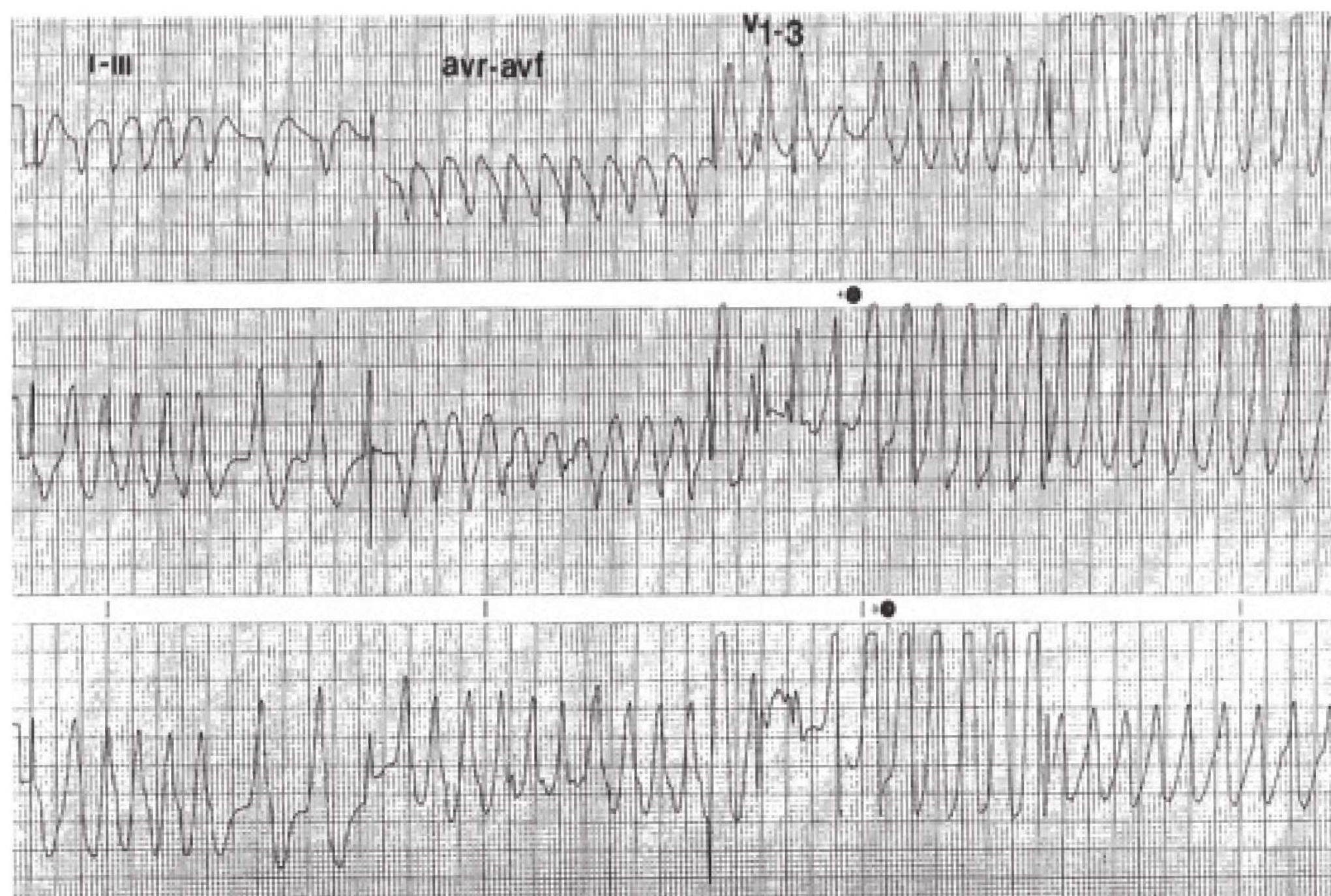


FIGURE 17-8

Preexcited atrial fibrillation (AF) due to conduction over a left free wall accessory pathway (AP). The electrocardiogram shows rapid irregular QRS complexes that represent fusion between conduction over the atrioventricular node and left free wall AP.

Shortest R-R intervals between preexcited QRS complexes of less than 250 ms, as in this case, indicate a risk of sudden death with this arrhythmia.

oral or intravenous verapamil, diltiazem, beta blockers, intravenous adenosine, and intravenous amiodarone are contraindicated. Preexcited tachycardias should be treated with electrical cardioversion or intravenous procainamide or ibutilide, which may terminate or slow the ventricular rate.

Management of patients with accessory pathways

Acute management of orthodromic AV reentry is discussed below for PSVT. Patients with WPW syndrome may have wide-complex tachycardia due to antidromic AV reentry, orthodromic AV with bundle branch block, or a preexcited tachycardia, and treatment depends on the underlying rhythm.

Initial patient evaluation should include assessment for aggravating factors, including intercurrent illness and factors that increase sympathetic tone. Examination should focus on excluding underlying heart disease. An echocardiogram is reasonable to exclude Ebstein's anomaly and hypertrophic cardiomyopathy.

Patients with preexcitation who have symptoms of arrhythmia are at risk for developing atrial fibrillation and sudden death if they have an AP with high-risk properties. The risk of cardiac arrest is in the range of 2 per 1000 patients in adults but is likely greater in children. An invasive electrophysiology study is warranted to determine if the AP is high enough risk to warrant potentially curative catheter ablation. For patients with concealed APs or known low-risk APs causing orthodromic AV reentry, chronic therapy is guided by symptoms and frequency of events. Vagal maneuvers may terminate episodes, as may a dose of beta blocker, verapamil, or diltiazem taken at the onset of an episode. Chronic therapy with these agents or flecainide can reduce the frequency of episodes in some patients. Catheter ablation is warranted for recurrent arrhythmias when drugs are ineffective, not tolerated, or not desired by the patient or if the AP is considered high risk (Fig. 17-8). Efficacy is in the range of 95% depending on the location of the AP. Serious complications occur in fewer than 3% of patients, but can include AV block, cardiac tamponade, thromboemboli, coronary artery injury, and vascular access complications. Mortality occurs in less than 1 in 1000 patients.

Adults who have preexcitation but no arrhythmia symptoms have a risk of sudden death estimated to be 1 per 1000 patient-years. Electrophysiology study is usually advised for people in occupations for which an arrhythmia occurrence would place them or others at risk, such as police, military, and pilots, or for individuals who desire evaluation for risk. Routine follow-up without therapy is reasonable in others. Children are at greater risk of sudden death, approximately 2 per 1000 patient-years.

TREATMENT Paroxysmal Supraventricular Tachycardia

Acute management of narrow QRS PSVT is guided by the clinical presentation. Continuous ECG monitoring should be implemented and a 12-lead ECG should always be obtained when possible. In the presence of hypotension with unconsciousness or respiratory distress, QRS-synchronous direct current cardioversion is warranted, but this is rarely needed, because intravenous adenosine works promptly in most situations (see below). For stable individuals, initial therapy takes advantage of the fact that most PSVTs are dependent on AV nodal conduction (AV nodal reentry or orthodromic AV reentry) and therefore likely to respond to sympatholytic and vagotonic maneuvers and drugs (Fig. 17-9). As these are administered, the ECG should be continuously recorded, because the response can establish the diagnosis. AV block with only transient slowing of tachycardia may expose ongoing p waves, indicating AT or atrial flutter as the mechanism.

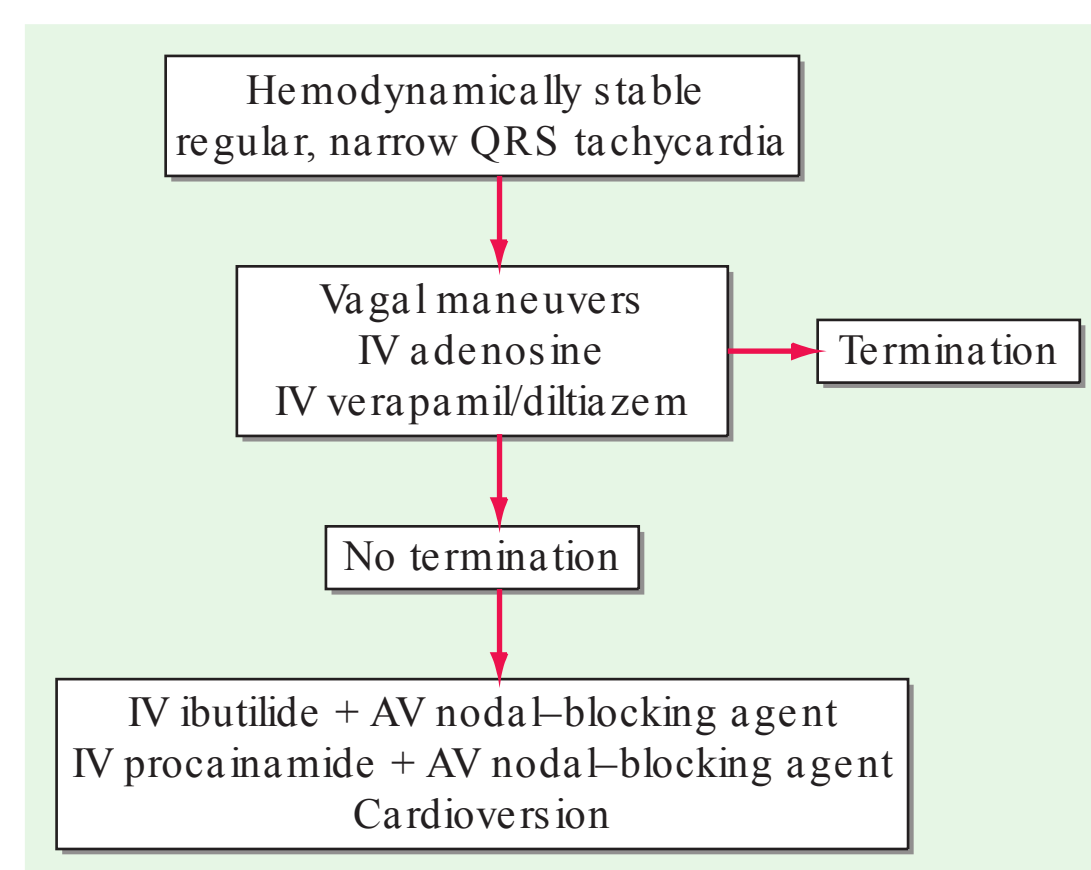


FIGURE 17-9

Treatment algorithm for patients presenting with hemodynamically stable paroxysmal supraventricular tachycardia. AV, atrioventricular.

Carotid sinus massage is reasonable provided the risk of carotid vascular disease is low, as indicated by absence of carotid bruits and no prior history of stroke. A Valsalva maneuver should be attempted in cooperative individuals, and if effective, the patient can be taught to perform this maneuver as needed. If vagal maneuvers fail or cannot be performed, intravenous adenosine will terminate the vast majority of PSVT by transiently blocking conduction in the AV node. Adenosine may produce transient chest pain, dyspnea, and anxiety. It is contraindicated in patients with prior cardiac transplantation due to potential hypersensitivity. It can theoretically aggravate bronchospasm. Adenosine precipitates atrial fibrillation, which is usually brief, in up to 15% of patients, so it should be used cautiously in patients with WPW syndrome in whom AF may produce hemodynamic instability. Intravenous beta blockers and calcium channel blockers (verapamil or

diltiazem) are also effective but may cause hypotension before and after arrhythmia termination and have a longer duration of action. These agents can also be given orally and can be taken by the patient on an as-needed basis to slow ventricular rate and facilitate termination by Valsalva maneuver.

The differential diagnosis of wide-complex tachycardia includes ventricular tachycardia (**Chap. 18**), PSVT with bundle branch block aberrancy, and preexcited tachycardia (see above). In general, these should be managed as ventricular tachycardia until proven otherwise. If the tachycardia is regular and the patient is stable, a trial of intravenous adenosine is reasonable. Very irregular wide-complex tachycardia should be managed with cardioversion, intravenous procainamide, or ibutilide, which presumes preexcited atrial fibrillation or flutter (see above). If the diagnosis of PSVT with aberrancy is unequivocal, as may be the case in patients with prior episodes, treatment for PSVT is reasonable. In all cases, continuous ECG monitoring should be implemented, and emergency cardioversion and defibrillation should be available.

COMMON ATRIAL FLUTTER AND MACROREENTRANT ATRIAL TACHYCARDIAS

Macroreentrant atrial tachycardia is due to a large reentry circuit, often associated with areas of scar in the atria. Common or typical right atrial flutter is due to a circuit that revolves around the tricuspid valve annulus, bounded anteriorly by the annulus and posteriorly by functional

conduction block in the crista terminalis. The wavefront passes through an isthmus between the inferior vena cava and the tricuspid valve annulus, known as the sub-Eustachian or cavotricuspid isthmus, where it is susceptible to interruption by catheter ablation. Thus, common atrial flutter is cavotricuspid isthmus-dependent atrial flutter. This circuit most commonly revolves in a counterclockwise direction (as viewed looking toward the tricuspid annulus from the ventricular aspect), which produces the characteristic negative sawtooth flutter waves in leads II, III, and aVF and positive P waves in lead V₁ (**Fig. 17-10**). When the direction is reversed, clockwise rotation produces the opposite P-wave vector in those leads. The atrial rate is typically 240–300 beats/min but may be slower in the presence of atrial disease or antiarrhythmic drugs. It often conducts to the ventricles with 2:1 AV block, creating a regular tachycardia at 150 beats/min, with p waves that may be difficult to discern. Maneuvers that increase AV nodal block will typically expose flutter waves, allowing diagnosis.

Common right atrial flutter often occurs in association with atrial fibrillation and with atrial scar from senescence or prior cardiac surgery. Some patients with atrial fibrillation that is treated with an antiarrhythmic drug, particularly flecainide, propafenone, or amiodarone, will present with atrial flutter rather than fibrillation.

Macroreentrant ATs that are not dependent on conduction through the cavotricuspid isthmus are referred to as atypical atrial flutters. They can occur in either atrium and are usually associated with areas of scar. Left

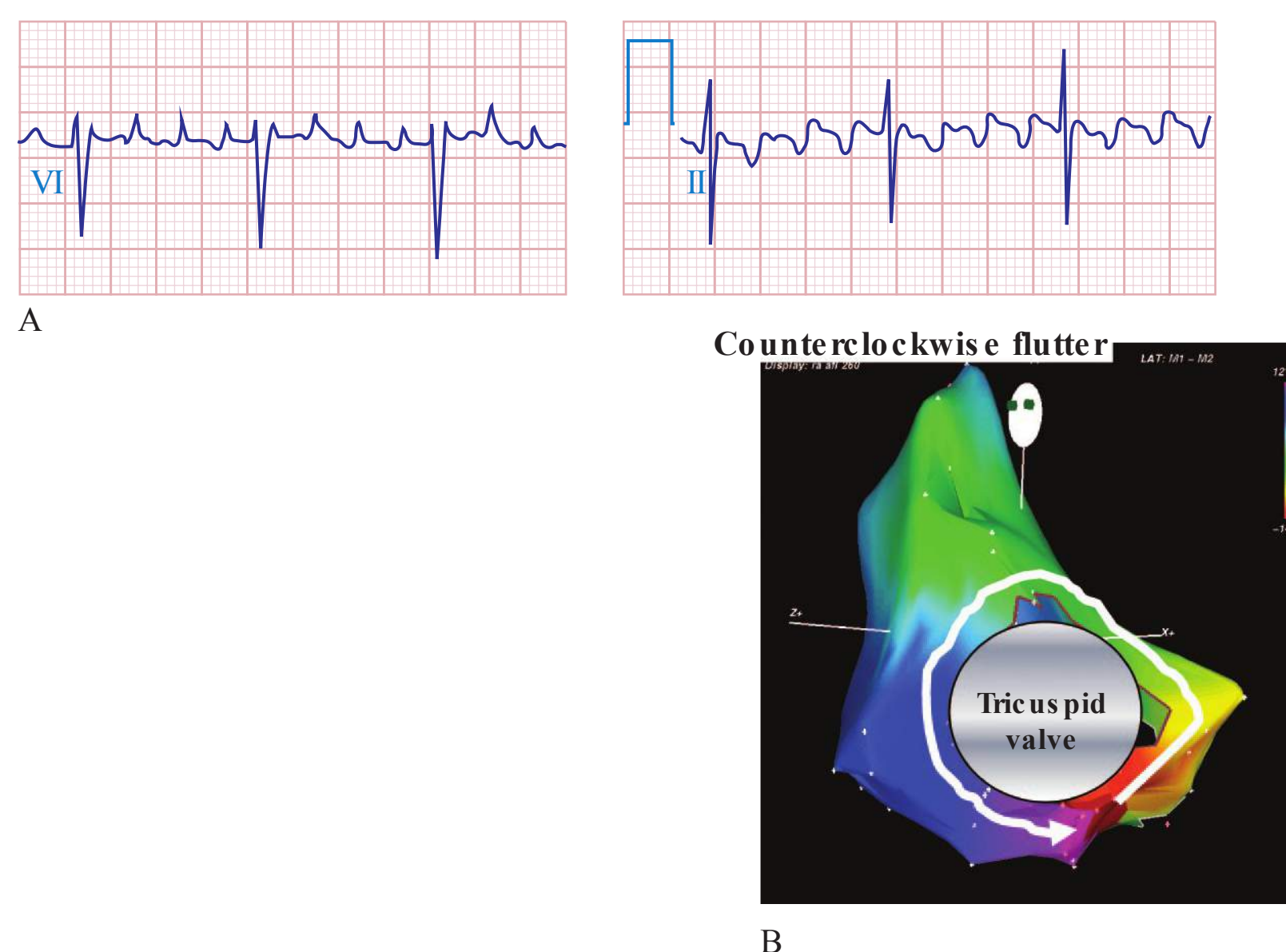


FIGURE 17-10

A. Common right atrial flutter, also known as cavotricuspid isthmus flutter, showing positive P waves in lead V₁ and negative “sawtooth” pattern in lead II typical of counterclockwise rotation relative to the tricuspid valve annulus. (Adapted from F Marchlinski: The tachyarrhythmias. In Longo DL et al [eds]: Harrison's

Principles of Internal Medicine, 18th ed. New York, McGraw-Hill, 2012, pp 1878–1900.) B. A right atrial map of common counterclockwise flutter is shown. Colors indicate activation time, progressing from red to yellow to green, blue, and purple. The reentry path parallels the tricuspid annulus.

atrial flutter and perimitral left atrial flutter are commonly seen after extensive left atrial ablation for atrial fibrillation or atrial surgery. The clinical presentation is similar to common atrial flutter, but with different P-wave morphologies. They can be difficult to distinguish from focal AT, and in most cases, the mechanism can only be confirmed by an electrophysiology study.

TREATMENT **Atrial Flutter and Macroreentrant Atrial Tachycardias**

Initial management of atrial flutter is similar to that for atrial fibrillation, discussed in more detail below. Electrical cardioversion is warranted for hemodynamic instability or severe

symptoms. Otherwise, rate control can be achieved with administration of AV nodal–blocking agents, but this is often more difficult than for atrial fibrillation. The risk of thromboembolic events is felt to be similar to that associated with atrial fibrillation. Anticoagulation is warranted prior to conversion for episodes more than 48 h in duration and chronically for patients at increased risk of thromboembolic stroke based on the CHA₂DS₂-VASc scoring system (Table 17-6).

For a first episode of atrial flutter, conversion to sinus rhythm with no antiarrhythmic drug therapy is reasonable. For recurrent episodes, antiarrhythmic drug therapy with sotalolol, dofetilide, disopyramide, and amiodarone may be considered, but more than 70% of patients experience recurrences. For recurrent episodes of common atrial flutter, catheter

TABLE 17-6

CHA ₂ DS ₂ -VASc RISK ASSESSMENT AND ORAL ANTICOAGULANTS				
RISK FACTORS		POINTS	CHA ₂ DS ₂ -VASc Score	Estimated Annual Stroke Rate ^a
C – congestive heart failure		1	0	0
H – hypertension		1	1	1.3%
A – age ≥75 y		2	2	2.2%
D – diabetes mellitus		1	3	3.2%
S – stroke or TIA, embolus		2	4	4.0%
V – vascular disease		1	5	6.7%
A – age 65–75 y		1	6–9	>9%
Sex – female		1		
ANTICOAGULANTS	MECHANISM	Excretion	DOSING CONSIDERATIONS	RISK/BENEFIT
Warfarin	Vitamin K antagonist	Liver	Adjusted to INR 2–3 Days to therapeutic effect Multiple drug/food interactions (e.g., amiodarone)	Major hemorrhage: 1% per year Intracranial hemorrhage: 0.1–0.6% per year Risk of bleeding increases with INR >3.5 Inexpensive
Dabigatranb	Thrombin inhibitor	Kidney CCr >30 mL/min CCr 15–30 mL/min	150 mg bid 75 mg bid P-glycoprotein substrate (inducers – rifampin, reduce concentration) (inhibitors – amiodarone, verapamil, dronedarone, quinidine), Proton pump inhibitors may reduce absorption	Onset of action within hours No reversal agent for bleeding
Rivaroxaban	Xa inhibitor	Kidney CCr ≥50 mL/min CCr 15–50 mL/min	P-glycoprotein substrate 20 mg daily 15 mg daily	No reversal agent for bleeding
Apixaban	Xa inhibitor	Kidney and liver Cr >1.5 mg/dL	P-glycoprotein substrate 2.5 mg bid	No reversal agent for bleeding

^aModified from GYLip et al: Lancet 379:648, 2012. bU.S. Food and Drug Administration recommended dosing; other regimens are available outside the United States.
Abbreviations: CCr, creatinine clearance; Cr, creatinine; INR, international normalized ratio; TIA, transient ischemic attack.

192 ablation of the cavotricuspid isthmus abolishes the arrhythmia in over 90% of patients with a low risk of complications that are largely related to vascular access and infrequent heart block. Approximately 50% of patients presenting with atrial flutter develop atrial fibrillation within the next 5 years.

MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal AT (MAT) is characterized by at least three distinct P-wave morphologies with rates typically between 100 and 150 beats/min. Unlike atrial fibrillation, there are clear isoelectric intervals between P waves (**Fig. 17-11**). The mechanism is likely triggered automaticity from multiple atrial foci. It is usually encountered in patients with chronic pulmonary disease and acute illness.

TREATMENT Multifocal Atrial Tachycardia

Therapy for MAT is directed at treating the underlying disease and correcting any metabolic abnormalities. Electrical cardioversion has no effect. The calcium channel blockers verapamil or diltiazem may slow the atrial and ventricular rate. Patients with severe pulmonary disease often do not tolerate beta blocker therapy. MAT may respond to amiodarone, but long-term therapy with this agent is usually avoided due to its toxicities, particularly pulmonary fibrosis.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is characterized by disorganized, rapid, and irregular atrial activation with loss of atrial contraction and with an irregular ventricular rate that is determined by AV nodal conduction (**Fig. 17-12**). In an untreated patient, the ventricular rate also tends to be rapid and variable, between 120 and 160 beats/min, but in some patients, it may exceed 200 beats/min. Patients with high vagal tone or AV nodal conduction disease may have slow rates.

AF is the most common sustained arrhythmia and is a major public health problem. Prevalence increases with age, and more than 95% of AF patients are older than 60 years of age. The prevalence by age 80 is approximately 10%. The lifetime risk of developing AF for individuals 40 years old is approximately 25%. AF is slightly more common in men than women and more common in whites than blacks. Risk factors for developing AF in addition to age include hypertension, diabetes mellitus, cardiac disease, and sleep apnea. AF is a marker for heart disease, the severity of heart disease, and age, and it is therefore difficult to determine the extent to which AF itself contributes to associated increased mortality and morbidity. AF is associated with increased risk of developing heart failure. AF increases the risk of stroke by fivefold and is estimated to be the cause of 25% of strokes. It also increases the risk of dementia.

AF is occasionally associated with an acute precipitating factor such as hyperthyroidism, acute alcohol intoxication, or an acute illness including myocardial infarction or pulmonary embolism. AF occurs in up to 30% of patients recovering from cardiac surgery, associated with inflammatory pericarditis.

The clinical type of AF suggests the underlying pathophysiology (**Fig. 17-12**). Paroxysmal AF is defined as episodes that start and stop spontaneously. It is often initiated by small reentrant or rapidly firing foci in sleeves of atrial muscle along the pulmonary veins. Catheter ablation that isolates these foci usually abolishes the AF. Persistent AF has a longer duration, exceeding 7 days, and, in many cases, will continue unless cardioversion is performed. Cardioversion can be followed by prolonged periods of sinus rhythm. Episodes may be initiated by rapidly firing foci, but persistence of the arrhythmia is likely due to single or multiple areas of reentry facilitated by structural and electrophysiologic atrial abnormalities. In patients with long-standing persistent AF (>1 year), significant structural changes are present in the atrium that support reentry and automaticity, making it difficult to restore and maintain sinus rhythm. Some patients progress over



FIGURE 17-11

Multifocal atrial tachycardia. Rhythm strip obtained from a patient with severe pulmonary disease during an acute illness. Arrows note three distinct P-wave morphologies.

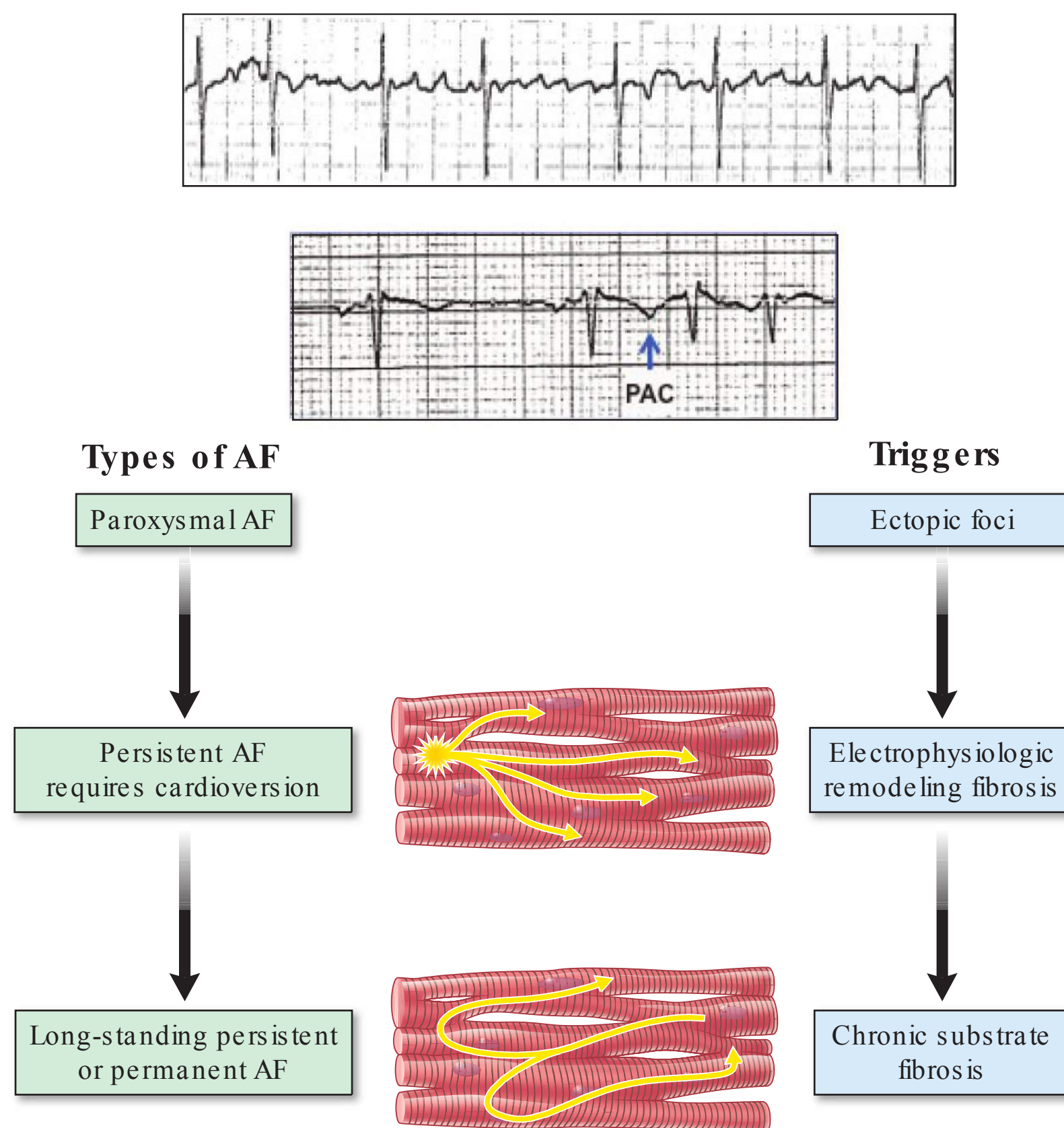


FIGURE 17-12

A rhythm strip of atrial fibrillation (AF) showing no distinct P-wave morphology and irregular ventricular response. Diagram depicts atrial fibrillation types. Paroxysmal AF is initiated by premature beats, as shown in the rhythm strip (arrow) after two sinus beats. Triggering foci are often an important cause of this

arrhythmia. Persistent AF is associated with atrial structural and electrophysiologic remodeling, as well as with triggering foci in many patients. Long-standing persistent AF is associated with greater structural remodeling with atrial fibrosis and electrophysiologic remodeling.

years from paroxysmal to persistent AF. Fibrosis that develops with aging and atrial hypertrophy in response to hypertension and other cardiac disease may be an important promoting factor, although electrophysiologic changes to conduction and refractoriness occur as well in response to chronic tachycardia in the atrium.

Clinical consequences are related to rapid ventricular rates, loss of atrial contribution to ventricular filling, and predisposition to thrombus formation in the left atrial appendage with potential embolization. Presentations vary with the ventricular rate and underlying heart disease and comorbidities. Many patients are asymptomatic. Rapid rates may cause hemodynamic collapse or heart failure exacerbations particularly in patients with impaired cardiac function, hypertrophic cardiomyopathy, and heart failure with preserved systolic function. Exercise intolerance and easy fatigability are common. Occasionally, dizziness or syncope occurs due to pauses when AF terminates to sinus rhythm (Fig. 17-13).

TREATMENT Atrial Fibrillation

Treatment for AF is primarily guided by patients' symptoms, the hemodynamic effect of AF, the duration of AF if there are persistent risk factors for stroke, and underlying heart disease. Oral anticoagulation in high-risk patients with AF includes vitamin K antagonists or the newer anticoagulants such as thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban), but not antiplatelet agents (aspirin and clopidogrel), which have substantially less effect.

New-onset AF that produces severe hypotension, pulmonary edema, or angina should be electrically cardioverted starting with a QRS synchronous shock of 200 J, ideally after sedation or anesthesia is achieved. Greater shock energy and different electrode placements may be tried if the shock fails to terminate AF. If AF terminates and reinitiates, administration of an antiarrhythmic drug, such as ibutilide, and repeat cardioversion may be considered. If the patient is stable, immediate management involves rate control to alleviate or prevent symptoms, anticoagulation if appropriate,

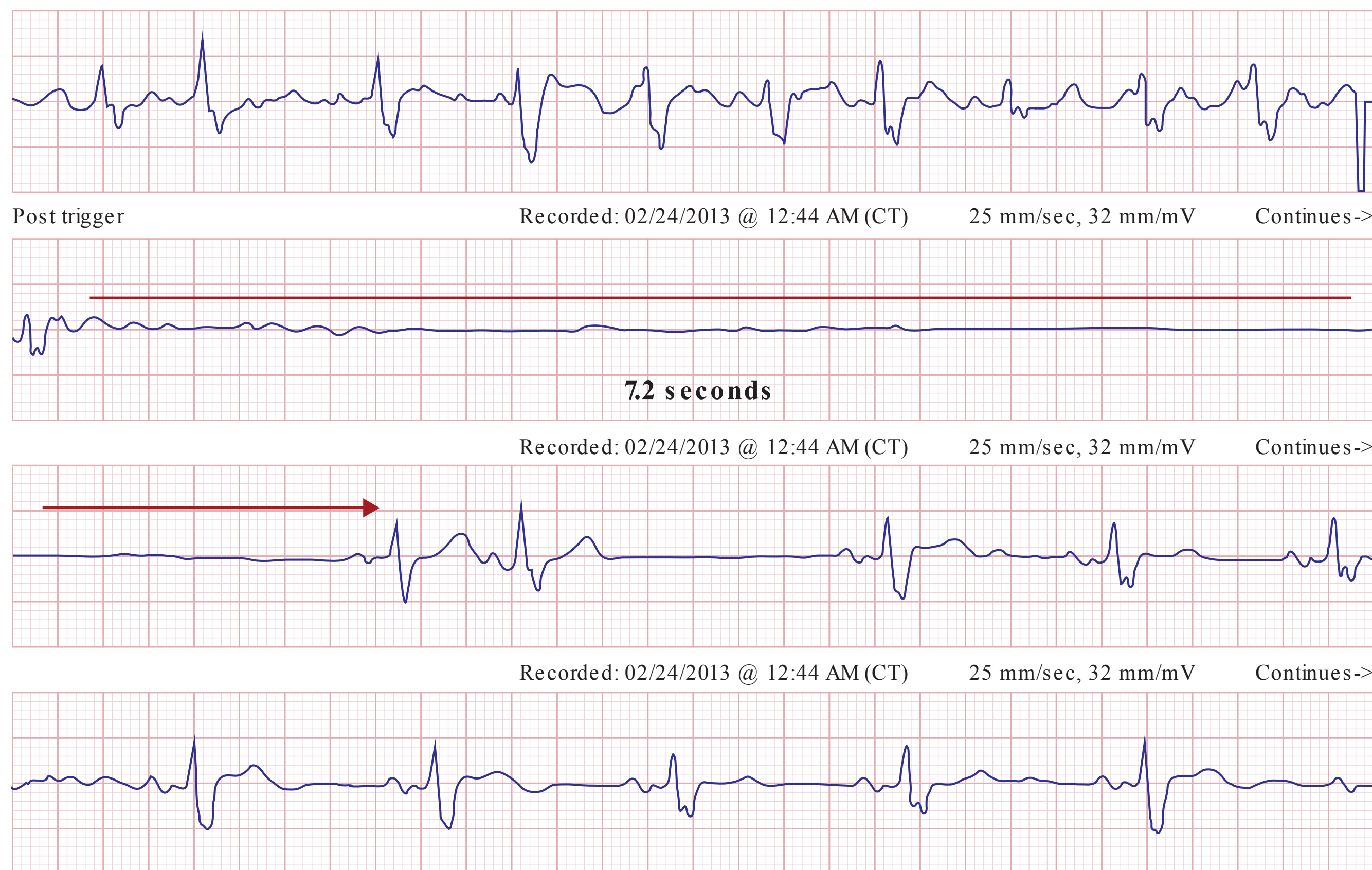


FIGURE 17-13

A continuous rhythm strip is shown. Atrial fibrillation is present at the top and abruptly terminates in the second tracing, with

atrial and ventricular standstill for 7.2 s until resumption of sinus rhythm. The patient experienced syncope.

and cardioversion to restore sinus rhythm if AF is persistent. Anticoagulation strategies for new-onset AF are debated. In the absence of contraindications, it is usually appropriate to initiate systemic anticoagulation with heparin immediately, while evaluation and other therapies are implemented.

CARDIOVERSION AND ANTICOAGULATION Cardioversion within 48 h of the onset of AF is common practice in patients who have not been anticoagulated, provided that they are not at high risk for stroke due to a prior history of embolic events, rheumatic mitral stenosis, or hypertrophic cardiomyopathy with marked left atrial enlargement. These patients are usually at risk of recurrence, such that initiation of anticoagulation is considered based on the patient's individual risk for stroke, commonly assessed from the CHA₂DS₂-VASc score.

If the duration of AF exceeds 48 h or is unknown, there is greater concern for thromboembolism with cardioversion, even in patients considered low risk for stroke. There are two approaches to mitigate the risk related to cardioversion. One option is to anticoagulate continuously for 3 weeks before and a minimum of 4 weeks after cardioversion. A second approach is to start anticoagulation and perform a transesophageal echocardiogram to determine if thrombus is present in the left atrial appendage. If thrombus is absent, cardioversion can be performed and anticoagulation

continued for a minimum of 4 weeks because recovery of atrial mechanical function after electrical or pharmacologic cardioversion may be delayed and thrombus can form and embolize days after cardioversion. Some patients may merit ongoing anticoagulation after cardioversion, depending on stroke risk profile.

RATE CONTROL Acute rate control can be achieved with beta blockers and/or the calcium channel blockers verapamil and diltiazem administered either intravenously or orally, as warranted by the urgency of the clinical situation. Digoxin may be added, particularly in heart failure patients, because it does not have negative inotropic effects, particularly if use of AV nodal-blocking agents is limited by poor tolerance or is contraindicated. Its effect is modest but synergistic with the other AV nodal-blocking agents, but it is particularly limited when sympathetic tone is elevated. Typically, the goal of acute rate control is to reduce the ventricular rate to less than 100/min, but the goal must be guided by the clinical situation.

CHRONIC RATE CONTROL For patients who remain in AF chronically, the goal of rate control is to alleviate and prevent symptoms and prevent deterioration of ventricular function from excessive rates. β -Adrenergic blockers, calcium channel blockers, and digoxin are used, sometimes in combination. Rate should be assessed with exertion and medications

adjusted accordingly. Exertion-related symptoms are often an indication of inadequate rate control. The initial goal is a resting heart rate of less than 80 beats/min that increases to less than 100 beats/min with light exertion, such as walking. If it is difficult to slow the ventricular rate to that degree, allowing a resting rate of up to 110 beats/min is acceptable provided it does not cause symptoms and ventricular function remains normal. Periodic assessment of ventricular function is warranted because some patients develop tachycardia-induced cardiomyopathy.

If adequate rate control in AF is difficult to achieve, further consideration should be given to restoring sinus rhythm. Catheter ablation of the AV junction to create heart block and implantation of a permanent pacemaker reliably achieve rate control without the need for AV nodal agents, but implement life-long permanent pacing. Right ventricular apical pacing induces dyssynchronous ventricular activation that can be symptomatic or depress ventricular function in some patients. Biventricular pacing may be used to minimize the degree of ventricular dyssynchrony.

STROKE PREVENTION IN ATRIAL FIBRILLATION The majority of patients warrant chronic anticoagulation, but selection of therapy should be individualized based on patient profile and risks and benefits of individual agents. Anticoagulation with a vitamin K antagonist is warranted for all patients with AF who have rheumatic mitral stenosis or mechanical heart valves for whom the newer anticoagulants have not been tested. Anticoagulation with a vitamin K antagonist (warfarin) or the newer oral anticoagulants is warranted for patients who have had more than 48 h of AF and are undergoing cardioversion, for patients who have a prior history of stroke, or for patients with a CHA₂DS₂-VASc score of ≥ 2 , but it may be considered in patients with a risk score of 1. The approach to patients with paroxysmal AF is the same as for persistent AF. It is recognized that many patients who appear to have infrequent AF episodes often have asymptomatic episodes that put them at risk. Absence of AF during periodic monitoring is not sufficient to indicate low risk. The role of continuous monitoring with implanted recorders or pacemakers is not yet clear as a guide for anticoagulation in patients with a borderline risk profile. Bleeding is the major risk of anticoagulation. Major bleeding requiring transfusion or in a critical area (e.g., intracranial) occurs in approximately 1% of patients per year. Risk factors for bleeding include age >65 –75 years, heart failure, history of anemia, and excessive alcohol or nonsteroidal anti-inflammatory drug use. Patients with coronary stents who require antiplatelet therapy with aspirin and a thienopyridine are at particularly high risk of bleeding.

Warfarin reduces the annual risk of stroke by 64% compared to placebo and by 37% compared to antiplatelet therapy. The newer anticoagulants, dabigatran, rivaroxaban, and apixaban, have been found to be noninferior to warfarin in individual trials, and analysis of pooled data suggests superiority to warfarin by small absolute margins of 0.4–0.7% in reduction of mortality, stroke, major bleeding, and

intracranial hemorrhage. Warfarin is an inconvenient agent that requires several days to achieve a therapeutic effect (prothrombin time [PT]/international normalized ratio [INR] >2), requires monitoring of PT/INR to adjust dose, and has many drug and food interactions, thus limiting patient compliance. The newer agents are easier to use and achieve reliable anticoagulation promptly without requiring dosage adjustment based on blood tests. Dabigatran, rivaroxaban, and apixaban have renal excretion, cannot be used with severe renal insufficiency, and require dose adjustment for modest renal impairment, which is of particular concern in the elderly, who are at increased bleeding risk. Excretion can also be influenced by P-glycoprotein inducers and inhibitors. Warfarin anticoagulation can be reversed by administration of fresh frozen plasma and vitamin K. Reversing agents for the newer anticoagulants are lacking (but in development), and bleeding must be managed with supportive care, with the expectation that clotting will improve over 12 h as the anticoagulant is excreted.

The antiplatelet agents aspirin and clopidogrel are inferior to warfarin for stroke prevention in AF and do not reduce the risk of bleeding. Clopidogrel combined with aspirin is better than aspirin alone but inferior to warfarin and has greater bleeding risk than aspirin alone.

Chronic anticoagulation is contraindicated in some patients due to bleeding risks. Because most atrial thrombi are felt to originate in the left atrial appendage, surgical removal of the appendage, combined with atrial maze surgery, may be considered for patients undergoing surgery, although removal of the appendage has not been unequivocally shown to reduce the risk of thromboembolism. Percutaneous devices that occlude or ligate the left atrial appendage are being studied for safety and efficacy.

RHYTHM CONTROL The decision to administer antiarrhythmic drugs or perform catheter ablation to attempt maintenance of sinus rhythm (commonly referred to as the “rhythm control strategy”) is mainly guided by patient symptoms and preferences regarding the benefits and risks of therapies. In general, patients who maintain sinus rhythm have better survival than those who continue to have AF. This is likely because continued AF is a marker of disease severity. In randomized trials, administration of antiarrhythmic medications to maintain sinus rhythm did not improve survival or symptoms compared to a rate control strategy, and the drug therapy group had more hospitalizations. Disappointing efficacy and toxicities of available antiarrhythmic drugs and patient selection bias may be factors that influenced the results of these trials. The impact of catheter ablation on mortality is not known. A rhythm control strategy is usually selected for patients with symptomatic paroxysmal AF, a first episode of symptomatic persistent AF, AF with difficult rate control, and AF that has resulted in depressed ventricular function or that aggravates heart failure. A rhythm control strategy is more likely to be favored in younger patients than in sedentary or elderly patients in whom rate control is usually easily achieved. Even

if sinus rhythm is apparently maintained, anticoagulation is recommended according to the CHA₂DS₂-VASc stroke risk profile because asymptomatic episodes of AF are common. Following a first episode of persistent AF, a strategy using AV nodal-blocking agents, cardioversion, and anticoagulation is reasonable, in addition to addressing possible aggravating factors, including hypertension, heart failure, and sleep apnea. If recurrences are infrequent, periodic cardioversion is reasonable.

Pharmacologic Therapy for Maintaining Sinus Rhythm The goal of pharmacologic therapy is to maintain sinus rhythm or reduce episodes of AF. Drug therapy can be instituted once sinus rhythm has been established or in anticipation of cardioversion. β -Adrenergic blockers and calcium channel blockers help control ventricular rate, improve symptoms, and possess a low-risk profile, but have low efficacy for preventing AF episodes. Risks and side effects of antiarrhythmic drugs are a major consideration in selecting therapy. Class I sodium channel-blocking agents (e.g., flecainide, propafenone, disopyramide) are options for subjects without significant structural heart disease, but they have negative inotropic and proarrhythmic effects that warrant avoidance in patients with coronary artery disease or heart failure. The class III agents sotalol and dofetilide can be administered to patients with coronary artery disease or structural heart disease but have approximately a 3% risk of inducing excessive QT prolongation and torsades des pointes. Dofetilide should be initiated only in a hospital with ECG monitoring, and many physicians take this approach with sotalol as well. Dronedarone increases mortality in patients with heart failure. All of these agents have modest efficacy in patients with paroxysmal AF, of whom approximately 30–50% will benefit. Amiodarone is more effective, maintaining sinus rhythm in approximately two-thirds of patients. It can be administered to patients with heart failure and coronary artery disease. Over 20% of patients experience toxicities during long-term therapy.

CATHETER AND SURGICAL ABLATION FOR ATRIAL FIBRILLATION Catheter ablation avoids antiarrhythmic drug toxicities but has procedural risks and requires an experienced center. For patients with previously untreated but recurrent paroxysmal AF, catheter ablation has similar efficacy to antiarrhythmic drug therapy and is superior to antiarrhythmic drugs for patients who have recurrent AF despite drug treatment.

The procedure involves cardiac catheterization, transatrial septal puncture, and radiofrequency ablation or cryoablation to electrically isolate the regions around the pulmonary veins, abolishing the effect of triggering foci to interact with the left atrial AF substrate. Extensive areas of ablation are required, and gaps in healed ablation areas necessitate a repeat procedure in 20–50% of patients. Sinus rhythm is maintained for more than 1 year after one procedure in approximately 60% of patients and in 70–80% of patients after multiple procedures. Some patients become more responsive to antiarrhythmic drugs.

There is a 2–7% risk of major complications, including stroke (0.5–1%), cardiac tamponade (1%), phrenic nerve paralysis, bleeding from femoral access sites, and fluid overload with heart failure, that can emerge 1–3 days after the procedure. It is important to recognize the potential for delayed presentation of some complications. Ablation within the pulmonary veins can lead to pulmonary vein stenosis, presenting weeks to months after the procedure with dyspnea or hemoptysis. Esophageal ulcers can form immediately after the procedure and may rarely lead to a fistula between the left atrium and esophagus (estimated incidence of 0.1%) that presents as endocarditis and stroke 10 days to 3 weeks after the procedure.

Catheter ablation is less effective for persistent AF. More extensive ablation is often required, including areas that likely support reentry in regions outside the pulmonary venous antra, but individual strategies are debated. More than one ablation procedure is often required to maintain sinus rhythm.

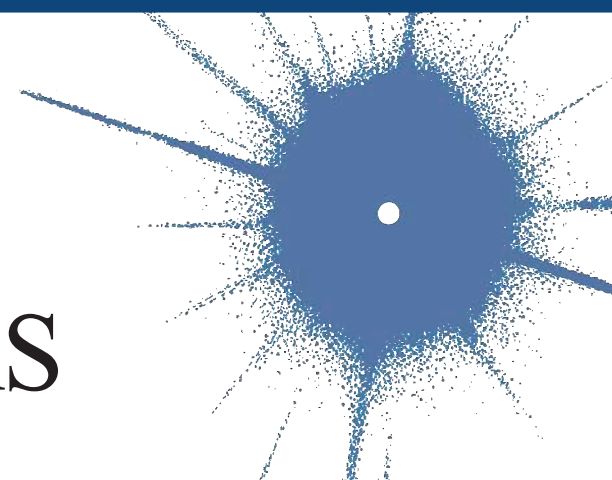
Surgical ablation of AF is typically performed concomitant with cardiac valve or coronary artery surgery and less commonly as a stand-alone procedure; however, for patients with persistent AF, surgical or hybrid procedures may have higher single-procedure efficacy. Risks include sinus node injury requiring pacemaker implantation. Surgical removal of the left atrial appendage may reduce stroke risk, although thrombus can form in the remnant of the appendage or if the appendage is not completely ligated.

Acknowledgment

Portions of this chapter were retained from the work of the previous author, Francis Marchlinski.

CHAPTER 18

VENTRICULAR ARRHYTHMIAS



Roy M. John ■ William G. Stevenson

Arrhythmias that originate in the ventricular myocardium or His-Purkinje system include premature ventricular beats, ventricular tachycardias that can be sustained or nonsustained, and ventricular fibrillation. Arrhythmia may emerge from a focus of myocardial or Purkinje cells capable of automaticity, or triggered automaticity, or from reentry through areas of scar or a diseased Purkinje system. Ventricular arrhythmias are often associated with structural heart disease and are an important cause of sudden death (**Chap. 35**). They also occur in some structurally normal hearts, in which case they are usually benign. Evaluation and management are guided by the risk of arrhythmic death, which is assessed based on symptoms, type of arrhythmia, and associated underlying heart disease.

DEFINITIONS

Ventricular arrhythmias are characterized by their electrocardiographic appearance and duration. Conduction away from the ventricular focus through the ventricular myocardium is slower than activation of the ventricles over the Purkinje system. Hence, the QRS complex during ventricular arrhythmias will be wide, typically >0.12 s.

Premature ventricular beats (also referred to as premature ventricular contractions [PVCs]) are single ventricular beats that fall earlier than the next anticipated supraventricular beat (**Fig. 18-1**). PVCs that originate from the same focus will have the same QRS morphology and are referred to as unifocal (**Fig. 18-1A**). PVCs that originate from different ventricular sites have different QRS morphologies and are referred to as multifocal (**Fig. 18-1B**). Two consecutive ventricular beats are ventricular couplets.

Ventricular tachycardia (VT) is three or more consecutive beats at a rate faster than 100 beats/min. Three or more consecutive beats at slower rates are designated an idioventricular rhythm (**Fig. 18-1C**). VT that

terminates spontaneously within 30 s is designated nonsustained (**Fig. 18-2**), whereas sustained VT persists longer than 30 s or is terminated by an active intervention, such as administration of an intravenous medication, external cardioversion, or pacing or a shock from an implanted cardioverter-defibrillator.

Monomorphic VT has the same QRS complex from beat to beat, indicating that the activation sequence is the same from beat to beat and that each beat likely originates from the same source (**Fig. 18-3A**). The initial site of ventricular activation largely determines the sequence of ventricular activation. Therefore, the QRS morphology of PVCs and monomorphic VT provides an indication of the site of origin within the ventricles (**Fig. 18-4**). The likely origin often suggests whether an arrhythmia is idiopathic or associated with structural disease. Arrhythmias that originate from the right ventricle or septum result in late activation of much of the left ventricle, thereby producing a prominent S wave in V_1 referred to as a left bundle branch block–like configuration. Arrhythmias that originate from the free wall of the left ventricle have a prominent positive deflection in V_1 , thereby producing a right bundle branch block–like morphology in V_1 . The frontal plane axis of the QRS is also useful. An axis that is directed inferiorly, as indicated by dominant R waves in leads II, III, and AVF, suggests initial activation of the cranial portion of the ventricle, whereas a frontal plane axis that is directed superiorly (dominant S waves in II, III, and AVF) suggests initial activation at the inferior wall.

Very rapid monomorphic VT has a sinusoidal appearance, also called ventricular flutter, because it is not possible to distinguish the QRS complex from the T wave (**Fig. 18-3B**). Relatively slow sinusoidal VTs have a wide QRS indicative of slowed ventricular conduction (**Fig. 18-3C**). Hyperkalemia, toxicity from excessive effects of drugs that blocks sodium channels

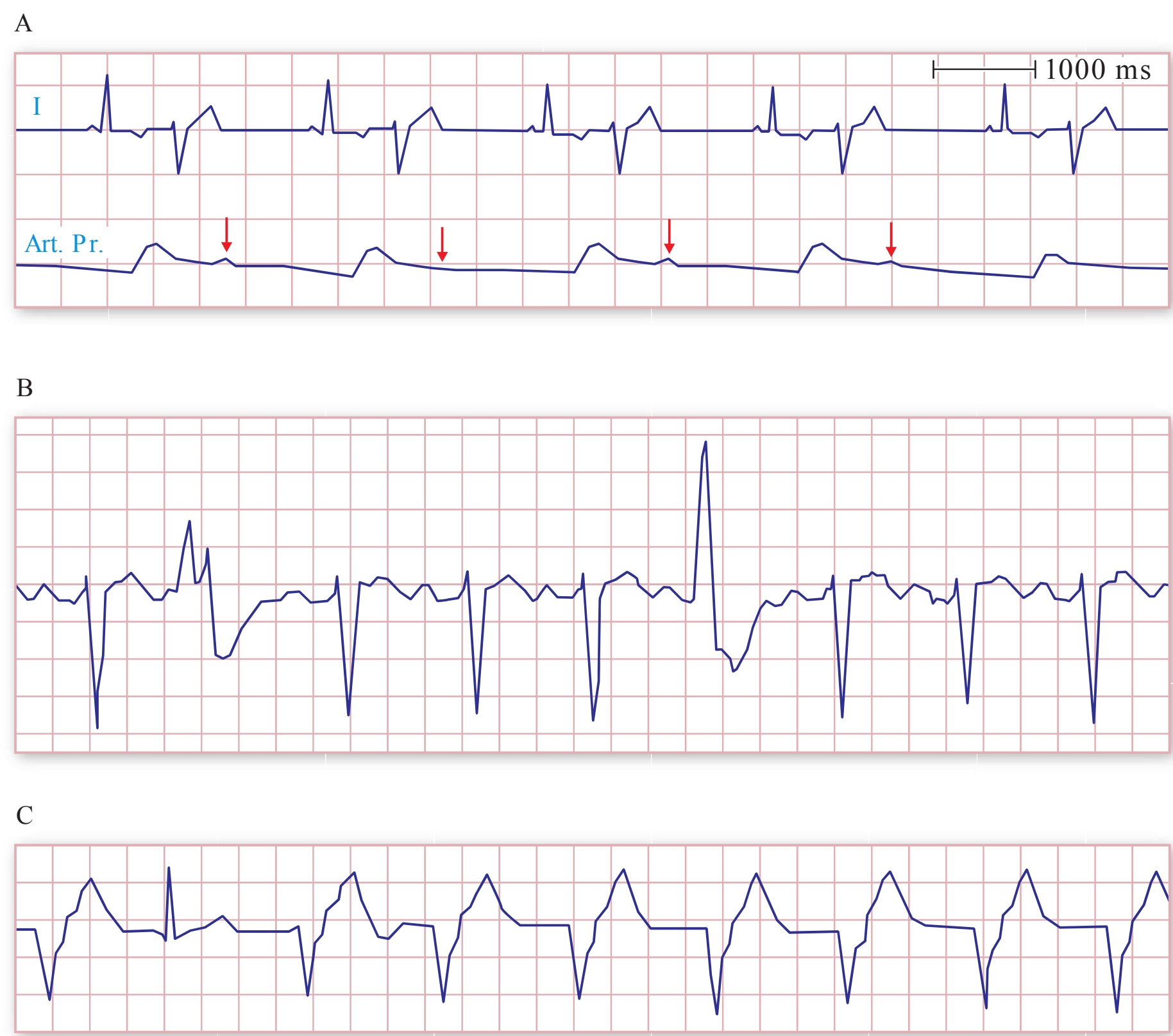


FIGURE 18-1
A. Unifocal PVCs follow every sinus beat in a bigeminal frequency. Trace shows electrocardiogram lead 1 and arterial pressure (Art. Pr.). Sinus rhythm beats are followed by normal arterial waveform. The arterial pressure following premature beats is attenuated (arrows) and imperceptible to palpation. The pulse in this patient is registered at half the heart rate. B. Multifocal PVCs. The two PVCs shown have different morphologies. C. Example of accelerated idioventricular rhythm. The second QRS is a normally conducted beat. All other QRS complexes on this rhythm strip are ventricular due to accelerated idioventricular rhythm.

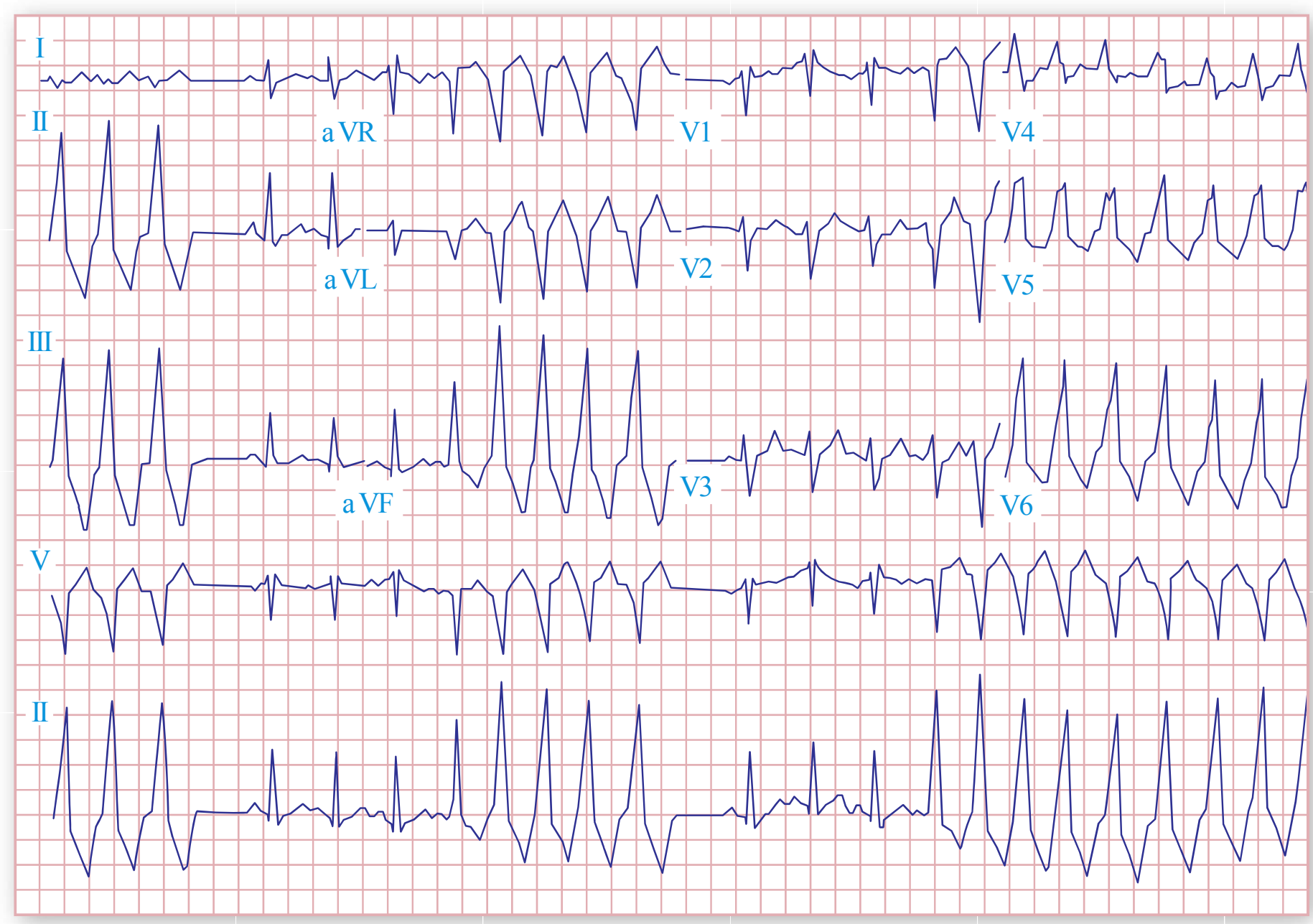


FIGURE 18-2
Repetitive monomorphic nonsustained ventricular tachycardia (VT) of right ventricular outflow tract origin. The VT has a left bundle branch block pattern with inferior axis with tall QRS complexes in the inferior leads.

(e.g., flecainide, propafenone, or tricyclic antidepressants), and severe global myocardial ischemia are causes.

Polymorphic VT has a continually changing QRS morphology indicating a changing ventricular activation sequence. Polymorphic VT that occurs in the context of congenital or acquired prolongation of the QT interval

often has a waxing and waning QRS amplitude creating a “twisting about the points” appearance referred to as Torsade de Pointes (Fig. 18-3D).

Ventricular fibrillation (VF) has continuous irregular activation with no discrete QRS complexes (Fig. 18-3E). Monomorphic or polymorphic VT may transition to VF in susceptible patients.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Common symptoms of ventricular arrhythmias include palpitations, dizziness, exercise intolerance, episodes of lightheadedness, syncope, or sudden death. These arrhythmias can be asymptomatic and encountered unexpectedly as an irregular pulse or heart sounds on examination, or seen on a routine electrocardiogram (ECG), exercise test, or cardiac ECG monitoring.

Syncope is a concerning symptom that can be due to an episode of VT with hypotension. Syncope due to a ventricular arrhythmia often indicates that there is a significant risk for subsequent cardiac arrest and sudden death with arrhythmia recurrence. Although benign causes of syncope, such as reflex-mediated neurocardiogenic (vasovagal) syncope and orthostatic hypotension, are generally more common, it is important to consider the possibility of heart disease or a genetic syndrome causing VT. When these are suspected, hospitalization for further evaluation and monitoring is often appropriate.

Sustained VT may present with cardiac arrest, often with degeneration of the VT to VF. Occasionally a sustained VT will be hemodynamically tolerated and present with diminished exercise capacity or exacerbation of heart failure. Many patients who are at risk for VT have known heart disease and may have an implantable cardioverter-defibrillator (ICD). In patients with an ICD, spontaneous episodes of VT may elicit an episode of transient lightheadedness, palpitations, or syncope that may be followed by a shock from the ICD (see below).

The diagnosis of ventricular arrhythmias is established by recording of the arrhythmia on an ECG or, in some cases, initiation of the arrhythmia during an electrophysiologic study (Table 18-1). A 12-lead ECG of the arrhythmia should be obtained when possible and often provides clues to the potential site of origin and possible presence of underlying heart disease (see above). When the arrhythmia is intermittent with days to weeks between symptoms, prolonged ambulatory monitoring to capture the ECG at the time of symptoms is required to make the diagnosis. Continuous ambulatory monitoring or looping event recording monitors are options. Exercise testing should be considered in patients with exercise-induced symptoms.

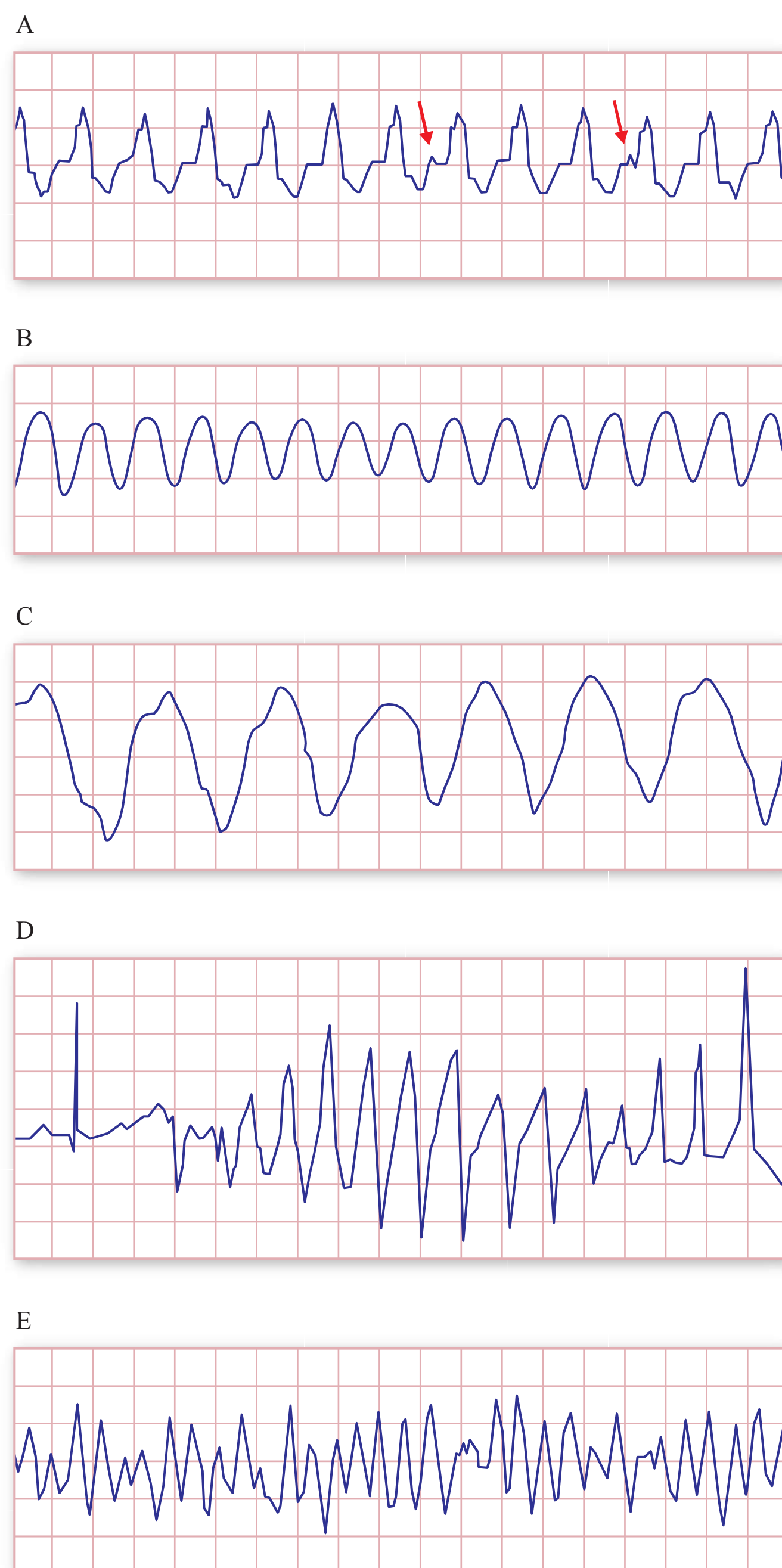


FIGURE 18-3

Examples of types of ventricular tachycardia (VT). A. Monomorphic VT with dissociated P waves (short arrows). B. Ventricular flutter. C. Sinusoidal VT due to electrolyte disturbance or drug effects. D. Polymorphic VT resulting from prolongation of QT interval (torsade de pointes VT). E. Ventricular fibrillation.

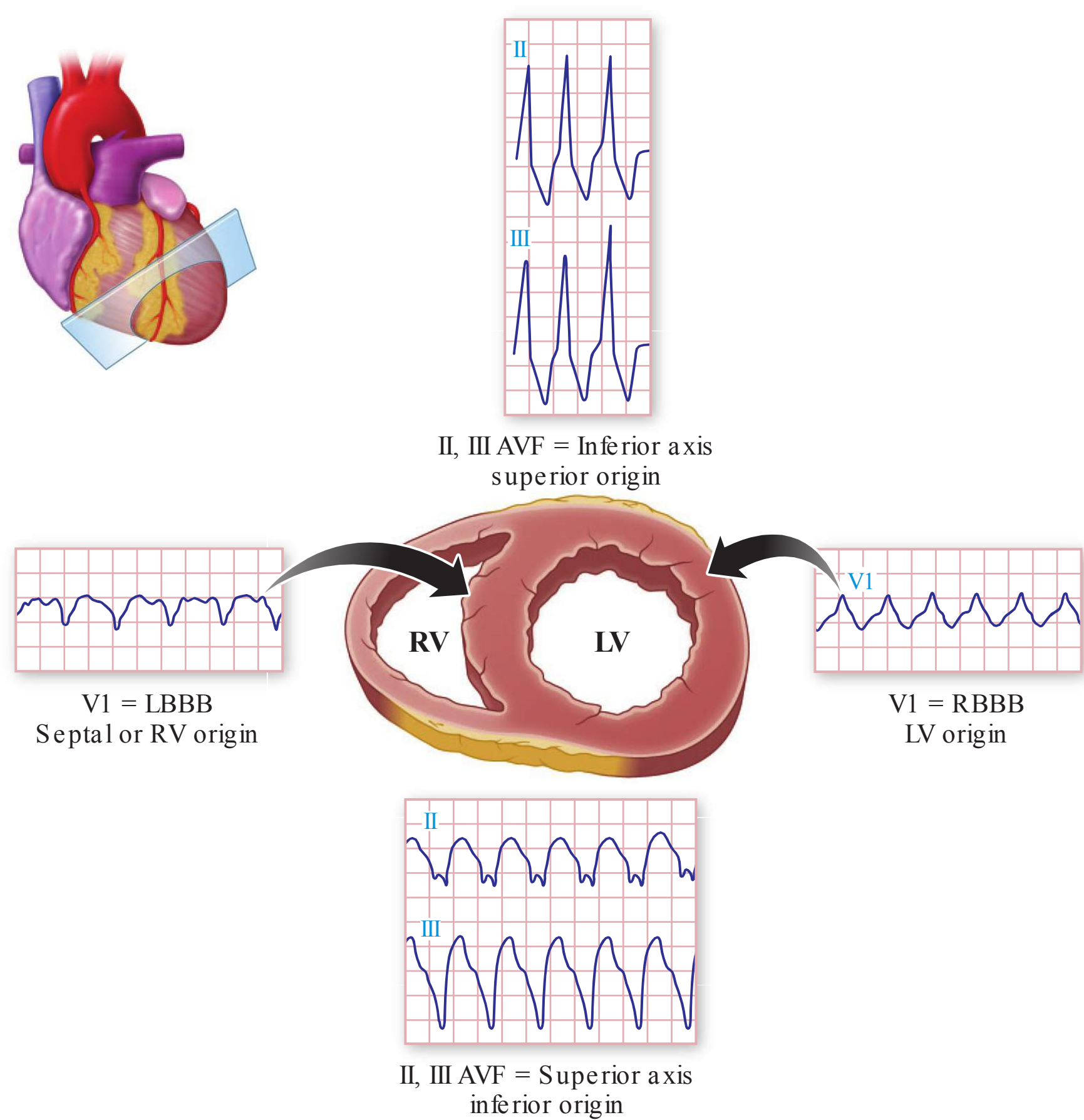


FIGURE 18-4
Site of VT origin based on QRS morphology. LBBB, left bundle branch block; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle.

TABLE 18-1

DIAGNOSTIC TESTS FOR VENTRICULAR ARRHYTHMIAS	
I. 12-Lead ECG	
A.	Should be obtained for PVCs, nonsustained VT, and monomorphic VT when possible
B.	QRS morphology suggests ventricular region of origin
V1 – dominant S	= septum or RV
V1 – dominant R	= LV
Superior axis	= inferior wall origin
Inferior axis	= outflow region or anterior wall
II. Ambulatory monitoring	
A.	24- to 48-h continuous Holter monitor
Useful for	evaluation of daily symptoms to quantitate PVCs
B.	Event recorder: can be used for weeks at a time
Useful for	evaluation of infrequent symptoms
Some require	patient activation and will miss asymptomatic arrhythmias
III. Exercise testing	
A.	Useful for evaluating exercise-induced arrhythmias and symptoms
B.	QT interval response to exercise may be abnormal in long QT syndrome
IV. Invasive electrophysiology study	
A.	Can establish definitive diagnosis of VT versus supraventricular tachycardia with aberrancy or ventricular preexcitation
B.	Can provoke some arrhythmias that are otherwise infrequent
C.	Allows potential catheter ablation
D.	Procedural risks determined by vascular access, whether ablation is performed, and the location of the arrhythmia substrate

Abbreviation: RV, right ventricle. See text for other abbreviations.

APPROACH TO THE PATIENT

Documented or Suspected Ventricular Arrhythmias

Initial assessment focuses on hemodynamic stability and evaluation for underlying heart disease. A family history of sudden death or cardiomyopathy suggests the possibility of a genetic basis for the arrhythmia and greater risk. The electrocardiogram can provide important clues. Patients with benign idiopathic arrhythmias usually have a completely normal ECG during sinus rhythm.

Cardiac imaging is warranted to assess ventricular function and look for evidence of depressed ventricular function indicative of a cardiomyopathy or ventricular hypertrophy that may indicate hypertrophic cardiomyopathy. Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement can detect areas of ventricular scar, which are usually present in patients who are at risk for sustained monomorphic VT (**Fig. 18-5**). Evaluation to exclude atherosclerotic coronary artery disease should be performed in patients at risk, guided by age and other risk factors.

SPECIFIC ARRHYTHMIAS

PVCs and nonsustained VT

Ventricular extrasystoles (**Fig. 18-1A**) can be due to automaticity or reentry (**Chap. 52**). PVCs can be a sign of increased sympathetic tone; myocardial ischemia; hypoxia; electrolyte abnormalities, particularly hypokalemia; or underlying heart disease. During myocardial ischemia or in association with other heart

disease, PVCs can be a harbinger of sustained VT or VF. In patients with heart disease, a higher frequency of ectopy and complexity (couplets and nonsustained VT) are associated with more severe disease and, in those with heart failure, with increased mortality. However, suppression of these arrhythmias with antiarrhythmic drugs does not improve survival. In the absence of cardiac disease, PVCs and nonsustained VT generally have a benign prognosis. PVCs that occur at a bigeminal frequency may not generate sufficient cardiac output for a radial pulse and hence may register at rates half that of the heart rate (**Fig. 18-1A**). Very frequent PVCs can depress ventricular function (see below).

Evaluation and management

When encountered during acute illness or as a new finding, evaluation should focus on detection and correction of potential aggravating factors and causes, specifically myocardial ischemia, ventricular dysfunction, and electrolyte abnormalities, most commonly hypokalemia. Underlying heart disease should be defined.

The ECG characteristics of the arrhythmia are often suggestive of whether structural heart disease is present. PVCs with smooth uninterrupted contours and sharp QRS deflections suggest an ectopic focus in relatively normal myocardium, whereas broad notching and slurred QRS deflections suggest a diseased myocardial substrate. The most frequent site of origin for idiopathic ventricular arrhythmias is the right ventricular outflow tract, giving rise to PVCs or VT that have a left bundle branch block configuration, with an inferiorly directed frontal plane axis as discussed below (**Fig. 18-2**). However, QRS morphology alone is not reliable as an indicator of disease or subsequent risk.

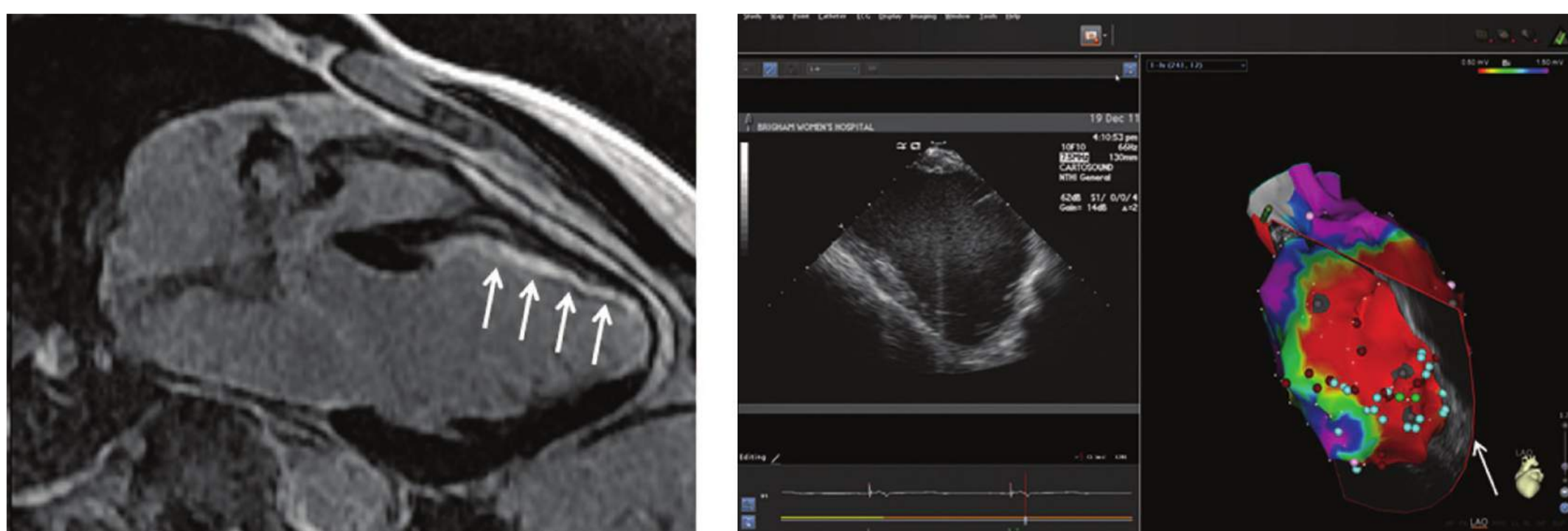


FIGURE 18-5

Imaging studies of the left ventricle (LV) used to assist ablation for ventricular tachycardia (VT). Left panel is a magnetic resonance image of a longitudinal section demonstrating thinning of the anterior wall and late gadolinium enhancement in a subendocardial scar (white arrows). The middle panel shows a two-dimensional image of the LV in long axis corresponding to the sector through the mid LV (arrow, right panel) obtained by an intracardiac echo probe positioned in the right ventricle. An

electroanatomic three-dimensional map of the LV in the left anterior oblique projection is displayed in the right panel. The purple color depicts areas of normal voltage (>1.5 mV). Blue, green, and yellow represent progressively lower voltages with the red areas indicating scar (<0.5 mV). Channels of viable myocardium with slow conduction within the scar are identified with the light blue dots. Areas of ablation delivered to regions involved in reentrant VT are indicated by maroon dots.

Nonsustained VT is usually monomorphic with rates less than 200 beats/min and typically lasts less than 8 beats (Fig. 18-2). Nonsustained VT that is very rapid, polymorphic, or with a first beat that occurs prior to the peak of the T wave (“short-coupled”) is uncommon and should prompt careful evaluation for underlying disease or genetic syndromes associated with sudden death.

A family history of sudden death should prompt evaluation for genetic syndromes associated with sudden death, including cardiomyopathy, long QT syndrome, and arrhythmogenic right ventricular cardiomyopathy (see below). Any abnormality on the 12-lead ECG warrants further evaluation (Fig. 18-6). Repolarization abnormalities are seen in a number of genetically determined syndromes associated with sudden death, including the long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy (ARVC), and hypertrophic cardiomyopathy. An echocardiogram is often necessary to assess ventricular function, wall motion abnormalities, and valvular heart disease. Cardiac magnetic resonance (CMR) imaging is also useful for this purpose and for the detection of ventricular scarring that is the substrate for sustained VT (Fig. 18-5). Exercise stress testing should be performed in patients with effort-related symptoms and in those at risk for coronary artery disease.

Idiopathic PVCs and nonsustained VT

For PVC and nonsustained VT in the absence of structural heart disease or a genetic sudden death syndrome, no specific therapy is needed unless the patient has

significant symptoms or evidence that frequent PVCs are depressing ventricular function (see below). Reassurance that the arrhythmia is benign is often sufficient to allow the patient to cope with the symptoms, which will often wax and wane in frequency over years. Avoiding stimulants, such as caffeine, is helpful in some patients. If symptoms require treatment, β -adrenergic blockers and nondihydropyridine calcium channel blockers (verapamil and diltiazem) are sometimes helpful (see Table 17-3). If these fail, more potent antiarrhythmic drugs or catheter ablation can be considered. The antiarrhythmic agents flecainide, propafenone, mexiletine, and amiodarone can be effective, but the potential for side effects warrants careful consideration. Catheter ablation can be effective if the arrhythmia occurs with sufficient frequency or is readily provoked such that its origin can be identified for ablation in a similar manner to that for idiopathic monomorphic VT as discussed below. Benefit must be carefully weighed against the procedure-related risks (see below).

PVCs and nonsustained VT associated with acute coronary syndromes

During and early after acute myocardial infarction (MI), PVCs and nonsustained VT are common and can be an early manifestation of ischemia and a harbinger of subsequent VF. Treatment with β -adrenergic blockers and correction of hypokalemia and hypomagnesemia reduce the risk of VF. Routine administration of the antiarrhythmic drugs such as lidocaine has not been shown to reduce mortality and is not indicated for suppression of PVCs or asymptomatic nonsustained VT.

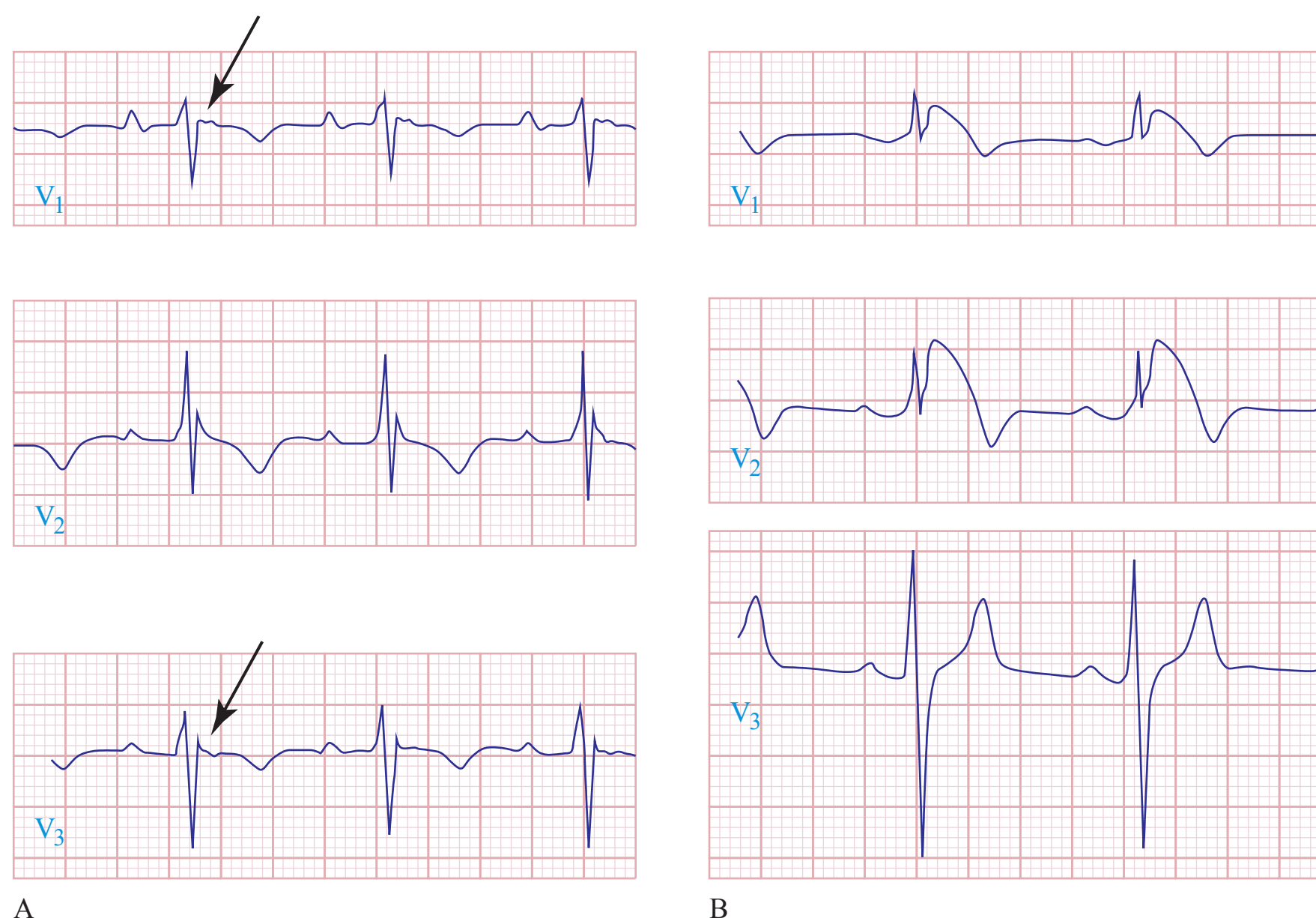


FIGURE 18-6

Precordial chest leads V_1 – V_3 showing typical abnormalities of arrhythmogenic right ventricular cardiomyopathy (ARVC) (A) and Brugada syndrome (B). In ARVC, there is T inversion and delayed ventricular activation manifest as epsilon waves (arrows).

Panel B shows ST elevation in V_1 and V_2 typical of the Brugada syndrome. (Figures reproduced from F Marchlinski: The tachyarrhythmias. In Longo DL et al [eds]: Harrison's Principles of Internal Medicine, 18th edition. New York, McGraw-Hill, 2012, pp 1878–1900.)

Following recovery from acute MI, frequent PVCs (typically >10 PVCs per hour), repetitive PVCs with couplets, and nonsustained VT are markers for depressed ventricular function and increased mortality, but routine antiarrhythmic drug therapy to suppress these arrhythmias is not warranted. Treatment with the sodium channel blocker flecainide increased mortality. Amiodarone therapy reduces sudden death, but does not improve total mortality. Therefore, amiodarone is an option for treatment of symptomatic arrhythmias in this population when the potential benefit outweighs its potential toxicities. β -Adrenergic blockers reduce sudden death but have limited effect on spontaneous arrhythmias.

For survivors of an acute MI, an ICD reduces mortality in certain high-risk groups: patients who have survived >40 days after the acute MI and have a left ventricular (LV) ejection fraction of ≤ 0.30 or who have an ejection fraction < 0.35 and have symptomatic heart failure (functional class II or III); and patients >5 days after MI who have a reduced LV ejection fraction, nonsustained VT, and inducible sustained VT or VF on electrophysiologic testing. ICDs do not reduce mortality when routinely implanted soon after MI or in patients after recent coronary artery revascularization surgery.

PVCs and nonsustained VT associated with depressed ventricular function and heart failure

PVCs and nonsustained VT are common in patients with depressed ventricular function and heart failure and are markers for disease severity and increased mortality, but antiarrhythmic drug therapy to suppress these arrhythmias has not been shown to improve survival. Antiarrhythmic drugs whose major action is blockade of the cardiac sodium channel (flecainide, propafenone, mexiletine, quinidine, and disopyramide) are avoided in patients with structural heart disease because of a risk of proarrhythmia, negative inotropic effects, and increased mortality. Therapy with the potassium channel blockers, e.g., dofetilide, does not reduce mortality. Amiodarone suppresses ventricular ectopy and reduces sudden death but does not improve overall survival. ICDs are the major therapy to protect against sudden death in patients at high risk and are recommended for those with LV ejection fraction < 0.35 and New York Heart Association class II and III heart failure, in whom they reduce mortality by 20%, from 36% to 29%, over 5 years.

Other cardiac diseases

Ventricular ectopy is associated with increased mortality in patients with hypertrophic cardiomyopathy (**Chap. 27**) or with congenital heart disease (**Chap. 22**) associated with right ventricular or LV dysfunction. In these patients, management is similar to that for patients with ventricular dysfunction. Pharmacologic

suppression of the arrhythmia has not been shown to improve mortality. ICDs are indicated for patients considered at high risk for sudden cardiac death.

PVC-induced ventricular dysfunction

Very frequent ventricular ectopy and repetitive nonsustained VT (Fig. 18-2) can depress ventricular function, possibly through an effect similar to chronic tachycardia or by inducing ventricular dyssynchrony. Depression of ventricular function rarely occurs unless PVCs account for more than 10–20% of total beats over a 24-h period. Often the PVCs are idiopathic and unifocal, most commonly originating from the LV papillary muscles or outflow tract regions where they can be targeted for ablation. The distinction between PVC-induced ventricular dysfunction as compared to a cardiomyopathic process causing ventricular dysfunction and arrhythmia is difficult and in some cases can be made only retrospectively by observing an improvement in ventricular function after the arrhythmia is suppressed with an antiarrhythmic drug, such as amiodarone, or by catheter ablation.

Idioventricular rhythms

Three or more ventricular beats at a rate slower than 100 beats/min are termed idioventricular rhythm (Fig. 18-1C). Automaticity is the likely mechanism. Idioventricular rhythms are common during acute MI (**Chap. 41**) and may emerge during sinus bradycardia. Atropine may be administered to increase the sinus rates if the loss of atrioventricular synchrony leads to hemodynamic compromise. This rhythm is also common in patients with cardiomyopathies or sleep apnea. It can also be idiopathic, often emerging when the sinus rate slows during sleep. Therapy should target any underlying cause and correction of bradycardia. Specific therapy for asymptomatic idioventricular rhythm is not necessary.

Sustained monomorphic VT

Sustained monomorphic VT presents as a wide QRS tachycardia that has the same QRS configuration from beat to beat, indicating an identical sequence of ventricular depolarization for each beat (Fig. 18-3A). VT originates from a stable focus or reentry circuit. In structural heart disease, the substrate is often an area of patchy replacement fibrosis due to infarction, inflammation, or prior cardiac surgery that creates anatomical or functional reentry pathways (Fig. 18-5). Less commonly, VT is related to reentry or automaticity in a diseased Purkinje system. In the absence of structural heart disease, idiopathic VT can present as sustained monomorphic VTs that are due to focal automaticity or reentry involving a portion of the Purkinje system.

The clinical presentation can vary depending on the rate of the arrhythmia, underlying cardiac function, and autonomic adaptation in response to the arrhythmia. Whereas patients with normal cardiac function might tolerate rapid VTs, those with severe LV dysfunction often experience symptoms of hypotension, even if VT is not particularly fast. Monomorphic VT may deteriorate to VF, which may be the initial cardiac rhythm recorded at the time of resuscitation.

Diagnosis

Sustained monomorphic VT has to be distinguished from other causes of uniform wide QRS tachycardia. These include supraventricular tachycardia with left or right bundle branch block aberrant conduction, supraventricular tachycardias conducted to the ventricles over an accessory pathway (**Chap. 17**), and rapid cardiac pacing in a patient with a pacemaker or defibrillator. In the presence of known heart disease, VT is the most likely diagnosis of a wide QRS tachycardia. Hemodynamic stability during the arrhythmia does not exclude VT. A number of ECG criteria have been evaluated. The presence of AV dissociation is usually a reliable marker for VT (**Fig. 18-7**), but P waves can be difficult to define. A P wave following each QRS does not exclude VT because 1:1 conduction from ventricle to atrium can occur. A monophasic R wave or Rs complex in AVR or concordance from V₁ to V₆ of monophasic R or S waves is also relatively specific for VT (**Fig. 18-7**). Other QRS morphology criteria have also been described, but all have limitations and are not very reliable in patients with severe heart disease.

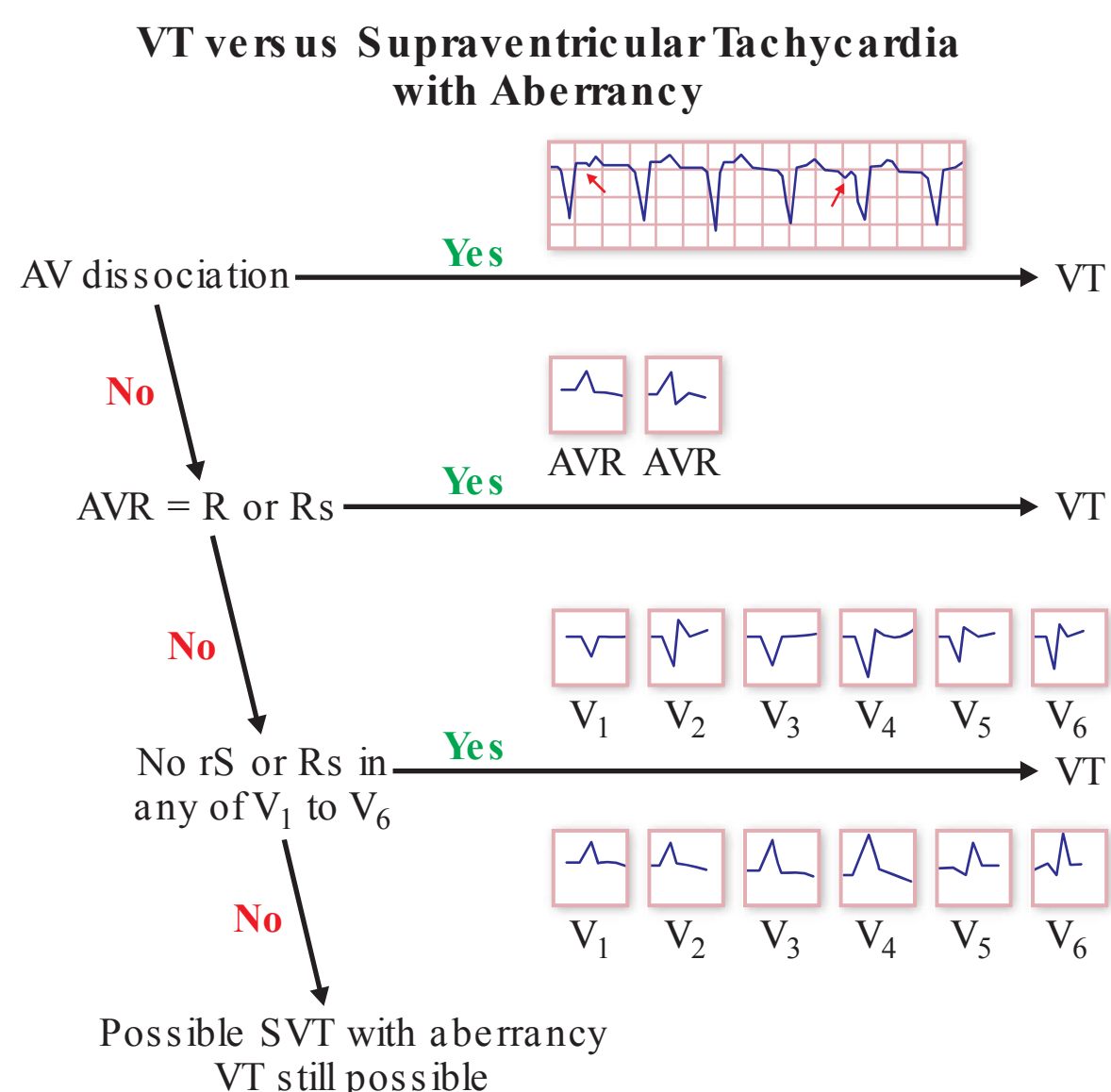


FIGURE 18-7

Algorithm for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia (SVT) with aberrancy. AV, atrioventricular.

In patients with known bundle branch block, the same QRS morphology during tachycardia as during sinus rhythm suggests supraventricular tachycardia rather than VT, but is not absolutely reliable. An electrophysiologic study is sometimes required for definitive diagnosis. Rarely, noise and movement artifacts on telemetry recordings can simulate VT; prompt recognition can avoid unnecessary tests and interventions.

When LV function is depressed or there is evidence of structural myocardial disease, scar-related reentry is the most likely diagnosis. Scars are suggested by pathologic Q waves on the ECG, segmental left or right ventricular wall motion abnormalities on echocardiogram or nuclear imaging, and areas of delayed gadolinium enhancement during MRI (**Fig. 18-5**).

Treatment and prognosis

Initial management follows Advanced Cardiac Life Support (ACLS) guidelines. If hypotension, impaired consciousness, or pulmonary edema is present, QRS synchronous electrical cardioversion should be performed, ideally after sedation if the patient is conscious. For stable tachycardia, a trial of adenosine is reasonable, as this may clarify a supraventricular tachycardia with aberrancy (**Chap. 17**). Intravenous amiodarone is the drug of choice if heart disease is present. Following restoration of sinus rhythm, hospitalization and evaluation to define underlying heart disease are required. Assessment of cardiac biomarkers for evidence of MI is appropriate, but acute MI is rarely a cause of sustained monomorphic VT, and elevations in troponin or creatine kinase (CK)-MB are more likely to indicate myocardial damage that is secondary to hypotension and ischemia from the VT. Subsequent management is determined by the underlying heart disease and frequency of VT. If VT recurs frequently or is incessant, administration of antiarrhythmic medications or catheter ablation may be required to restore stability. More commonly, sustained monomorphic VT occurs as an isolated episode, but with a risk of recurrence. ICDs are usually considered for VT associated with structural heart disease.

Sustained monomorphic VT in specific diseases

Coronary artery disease

Patients who present with sustained VT associated with coronary artery disease typically have a history of prior large MI and present years after the acute infarct with a remodeled ventricle and markedly depressed LV function. Even when there is biomarker evidence of acute MI, a preexisting scar from previous MI should be suspected as the cause of the VT. Infarct scars provide a durable substrate for sustained VT, and up to 70% of patients have a recurrence of the arrhythmia within 2 years. Scar-related reentry is not dependent on

recurrent acute myocardial ischemia, so coronary revascularization cannot be anticipated to prevent recurrent VT, even when it may be appropriate for other indications. Depressed ventricular function, which is a risk factor for sudden death, is usually present. Implantation of an ICD is warranted for most patients provided that there is a reasonable expectation of survival with acceptable functional status for the next year after recovery from the VT episode. ICDs reduce annual mortality from 12.3% to 8.8% and lower arrhythmic deaths by 50% in patients with hemodynamically significant sustained VT or a history of cardiac arrest compared with pharmacologic therapy. Chronic amiodarone therapy may be considered for patients who are not candidates for or who decline ICD placement.

Following ICD implantation, patients remain at risk for heart failure, recurrent ischemic events, and recurrent VT, with a 5-year mortality that exceeds 30%. Attention to therapies with survival benefit, including β -adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and statins, is important. Patients with frequent symptomatic recurrences of VT require antiarrhythmic drug therapy or catheter ablation.

Nonischemic dilated cardiomyopathy

Sustained monomorphic VT associated with nonischemic cardiomyopathy is usually due to scar-related reentry. The etiology of scar is often unclear, but progressive replacement fibrosis is the likely cause. On cardiac MRI, scars are detectable as areas of delayed gadolinium enhancement and are more often intramural or subepicardial in location as compared with patients with prior MI. Scars that cause VT are often located adjacent to a valve annulus and can occur in either ventricle. Any cardiomyopathic process can cause scars and VT, but cardiac sarcoidosis and Chagas' disease (**Chap. 33**) are particularly associated with monomorphic VT (**Table 18-2**). An ICD is usually indicated with additional drugs or ablation for control of recurrent VT.

Monomorphic VT in ARVC

ARVC (**Chap. 27**) is a rare genetic disorder most commonly due to mutations in genes encoding for cardiac desmosomal proteins. Approximately 50% have a familial transmission with autosomal dominant inheritance. A less common, autosomal recessive form is associated with cardiocutaneous syndromes that include Naxos disease and Carvajal syndrome. Patients typically present between the second and fifth decade with palpitations, syncope, or cardiac arrest owing to sustained monomorphic VT, although polymorphic VT can also occur. Fibrosis and fibro-fatty replacement most commonly involve the right ventricular myocardium and provide the substrate for reentrant VT that usually has a left bundle branch block–like configuration, consistent with the right ventricular origin. The sinus rhythm ECG

TABLE 18-2

VENTRICULAR ARRHYTHMIAS ASSOCIATED WITH DIFFERENT FORMS OF HEART DISEASE

I. Idiopathic VT without structural heart disease
A. Outflow tract origin
1. RV outflow tract: left bundle branch block pattern with inferior axis (tall QRS in inferior leads) and late transition in the precordial leads
2. LV outflow tract: prominent R in V_1 with inferior axis
B. Left posterior fascicular VT
1. Right bundle branch block pattern with left axis deviation (most common)
II. Ischemic cardiomyopathy
A. Monomorphic VT is common with prior large myocardial infarction
B. Polymorphic VT and VF should prompt ischemia evaluation
III. Nonischemic cardiomyopathy
A. Polymorphic VT and VF more common but fibrotic scars can cause monomorphic VT especially with sarcoidosis and Chagas' disease
IV. Arrhythmogenic right ventricular cardiomyopathy
A. Monomorphic VT usually of right ventricular origin (left bundle branch morphology)
B. Polymorphic VT and VF can occur independently or through degeneration of monomorphic VT
V. Repaired tetralogy of Fallot
A. Monomorphic VT of right ventricular origin (usually left bundle branch morphology)
VI. Hypertrophic cardiomyopathy
A. Polymorphic VT or ventricular fibrillation
B. Less commonly, monomorphic VT associated with myocardial scars
VIII. Genetic arrhythmia syndromes
A. Long QT syndrome: torsade de pointes VT
B. Brugada syndrome: VF
C. Catecholaminergic polymorphic VT: polymorphic VT or bidirectional VT
D. Short QT syndrome: ventricular fibrillation
E. Early repolarization syndrome: polymorphic VT or VF

Abbreviation: RV, right ventricle. See text for other abbreviations.

suggests the disease in more than 85% of patients, most often showing T-wave inversions in V_1 – V_3 (Fig. 18-6). Delayed activation of the right ventricle may cause a widened QRS (≥ 110 ms) in the right precordial leads and a prolonged S-wave upstroke in those leads, and occasionally a deflection at the end of the QRS known as an epsilon wave (Fig. 18-6). Cardiac imaging may show right ventricular enlargement or areas of abnormal motion or reveal areas of scar on CMR imaging with gadolinium. The monomorphic VT of early ARVC can sometimes be difficult to differentiate from idiopathic right ventricular outflow tract VT.

LV involvement can occur and occasionally precede manifest right ventricular disease. Heart failure is rare except in late stages, and survival to advanced age can

be anticipated provided that VT can be controlled. An ICD is recommended. When VT is exercise-induced, it may respond to β -adrenergic blockers and limiting exercise. Sotalol, amiodarone, and catheter ablation have been used to reduce recurrences. Ablation targets are often located in the subepicardium of the RV.

Tetralogy of fallot

VT occurs in 3–14% of patients late after repair of tetralogy of Fallot (**Chap. 22**) and contributes to a 2% per decade risk of sudden death. Monomorphic VT is due to reentry around areas of surgically created scar in the RV (Table 18-2). Factors associated with VT risk include age >5 years at the time of repair, high-grade ventricular ectopy, inducible VT on an electrophysiologic study, abnormal right ventricular hemodynamics, and sinus rhythm QRS duration >180 ms. An ICD is usually warranted for patients who have a spontaneous episode of VT, but criteria for a prophylactic ICD in other patients have not been established. Catheter ablation is used to control recurrent episodes.

Bundle branch reentry VT

Reentry through the Purkinje system occurs in approximately 5% of patients with monomorphic VT in the presence of structural heart disease. The reentry circuit typically revolves retrograde via the left bundle and anterograde down the right bundle, thereby producing VT that has a left bundle branch block configuration. Catheter ablation of the right bundle branch abolishes this VT. Bundle branch reentry is usually associated with severe underlying heart disease. Other scar-related VTs are often present and often require additional therapy or ICD implantation.

Idiopathic monomorphic VT

Idiopathic VT in patients without structural heart disease usually presents with palpitations, lightheadedness, and occasionally syncope, often provoked by sympathetic stimulation during exercise or emotional upset. The QRS morphology of the arrhythmia suggests the diagnosis (see below). The sinus rhythm ECG is normal. Cardiac imaging shows normal ventricular function and no evidence of ventricular scar. Occasionally a patient with structural heart disease is found to have concomitant idiopathic VT, unrelated to the structural disease. Sudden death is rare.

Outflow tract VTs originate from a focus, usually with features consistent with triggered automaticity. The arrhythmia may present with sustained VT, non-sustained VT, or PVCs often provoked by exercise or emotional upset. Repeated bursts of nonsustained VTs, which may occur incessantly, are known as repetitive monomorphic VTs and can cause tachycardia-induced cardiomyopathy with depressed ventricular function that recovers after suppression of the arrhythmia (Fig. 18-2). Most originate in the right ventricular

outflow tract, which gives rise to VT that has a left bundle branch block configuration in V_1 and an axis that is directed inferiorly, with tall R waves in leads II, III, and AVF (Fig. 18-2). Idiopathic VT can also arise in the LV outflow tract or in sleeves of myocardium that extend along the aortic root. LV origin is suspected when lead V_1 or V_2 has prominent R waves. Although this typical outflow tract QRS morphology favors idiopathic VT, some cardiomyopathies, notably ARVC, can cause PVCs or VT from this region. Excluding these diseases is an initial focus of evaluation.

LV intrafascicular VT presents with sustained VT that has a right bundle branch block–like configuration. It is often exercise-induced and occurs more often in men than women. The mechanism is reentry in or near the septal ramifications of the LV Purkinje system. This VT can be terminated by intravenous administration of verapamil.

Management of idiopathic VT

Treatment is required for symptoms or when frequent or incessant arrhythmias depress ventricular function. β -Adrenergic blockers are first-line therapy. Nondihydropyridine calcium channel blockers (diltiazem and verapamil) are sometimes effective. Catheter ablation is warranted for severe symptoms or when beta blockers or calcium channel blockers are not effective or not desired. Efficacy and risks of catheter ablation vary with the specific site of origin of the VT, being most favorable for arrhythmias originating in the right ventricular outflow tract.

LV fascicular VT can be terminated by intravenous administration of verapamil, although chronic therapy with oral verapamil is not always effective. Catheter ablation is recommended if β -adrenergic blockers or calcium channel blockers are ineffective or not desired.

Polymorphic VT

Sustained polymorphic VT can be seen with any form of structural heart disease (Table 18-2). However, unlike sustained monomorphic VT, polymorphic VT does not always indicate a structural abnormality or focus of automaticity. Reentry with continually changing reentrant paths, spiral wave reentry, and multiple automatic foci are potential mechanisms (**Chap. 52**). Sustained polymorphic VT usually degenerates into VF. Polymorphic VT is typically seen in association with acute MI or myocardial ischemia, ventricular hypertrophy, and a number of genetic mutations that affect cardiac ion channels (**Table 18-3**).

Polymorphic VT associated with acute MI/myocardial ischemia

Acute MI or ischemia is a common cause of polymorphic VT and should be the initial consideration in management. Approximately 10% of patients with

TABLE 18-3

CAUSES OF QT PROLONGATION AND TORSADE DE POINTES VENTRICULAR TACHYCARDIA

1. Congenital long QT syndromes (see text for details)	Antihistamines (histamine 1-receptor antagonists)
Long QT syndrome type 1: Reduced repolarizing current I_{Ks} due to mutation in KCNQ1 gene	Terfenadine, astemizole, diphenhydramine, hydroxyzine
Long QT syndrome type 2: Reduced repolarizing current I_{Kr} due to mutation in KCNH2 gene	Cholinergic antagonists: Cisapride, organophosphates
Long QT syndrome type 3: Delayed inactivation of the I_{Na} due to mutations in SCN5A gene	Citrate (massive blood transfusions)
Others: Several other types of long QT syndromes have been described; long QT types 1, 2, and 3 account for 80–90% of cases	Cocaine
2. Acquired prolongation of QT interval	Methadone
Electrolyte abnormalities	Fluoxetine (in conjunction with other drugs that prolong QT)
Hypokalemia	Cardiac conditions
Hypomagnesemia	Myocardial ischemia and infarction
Hypocalcemia	Myocarditis
Drugs	Marked bradycardia
Antiarrhythmic drugs	Stress cardiomyopathy
Class IA: Quinidine, disopyramide, procainamide	Endocrine disorders
Class III: Sotalol, amiodarone (QT prolongation common but torsade ventricular tachycardia is rare), ibutilide, dofetilide, almokalant	Hypothyroidism
Antibiotics	Hyperparathyroidism
Macrolides: Erythromycin, clarithromycin, azithromycin	Pheochromocytoma
Fluoroquinolones: Levofloxacin, moxifloxacin, gatifloxacin	Hyperaldosteronism
Trimethoprim-sulfamethoxazole	Intracranial disorders
Clindamycin	Subarachnoid hemorrhage
Pentamidine	Thalamic hematoma
Chloroquine	Cerebrovascular accident
Antifungals: Ketoconazole, itraconazole	Encephalitis
Antivirals: Amantadine	Head injury
Antipsychotics	Nutritional disorders
Haloperidol, phenothiazines, thioridazine, trifluoperazine, sertindole, zimelidine, ziprasidone	Anorexia nervosa
Tricyclic and tetracyclic antidepressants	Starvation
	Liquid protein diets
	Gastroplasty and ileojejunal bypass
	Celiac disease

acute MI develop VT that degenerates to VF, related to reentry through the infarct border zone. The risk is greatest in the first hour of acute MI. Following resuscitation as per the ACLS guidelines, management is as for acute MI (**Chap. 41**). β -Adrenergic blockers, correction of electrolyte abnormalities, and prompt myocardial reperfusion are required. Repeated episodes of polymorphic VT suggest ongoing myocardial ischemia and warrant assessment of adequacy of myocardial reperfusion. Polymorphic VT and VF that occur within the first 48 h of acute MI are associated with greater in-hospital mortality, but those who survive past hospital discharge are not at increased risk for arrhythmic sudden death. Long-term therapy for postinfarct ventricular arrhythmia is determined by residual LV function, with an ICD being indicated for persistent severe LV dysfunction (LV ejection fraction <0.35).

Repolarization abnormalities and genetic arrhythmia syndromes

Acquired long QT

Abnormal prolongation of the QT interval is associated with the polymorphic VT Torsade de Pointes

(**Fig. 18-8**). The VT often has a characteristic initiation sequence of a premature ventricular beat that induces a pause, followed by a sinus beat that has a longer QT interval and interruption of the T wave by the PVC that is the first beat of the polymorphic VT. This characteristic initiation is termed “pause-dependent” (Fig. 18-8). Causes of QT prolongation include electrolyte abnormalities, bradycardia, and a number of medications that block repolarizing potassium currents, notably the antiarrhythmic drugs sotalol, dofetilide, and ibutilide, but also a number of other medications used for noncardiac diseases, including erythromycin, pentamidine, haloperidol, phenothiazines, and methadone (Table 18-3). Individual susceptibility may be related to genetic polymorphisms or mutations that influence repolarization.

Patients typically present with near-syncope, syncope, or cardiac arrest. Sustained episodes degenerate to VF requiring defibrillation. PVCs and nonsustained VT often precede episodes of sustained VT. Intravenous administration of 1–2 g of magnesium sulphate usually suppresses recurrent episodes. If magnesium alone is ineffective, increasing heart rate with isoproterenol infusion or pacing, to a rate of 100–120 beats/min as required

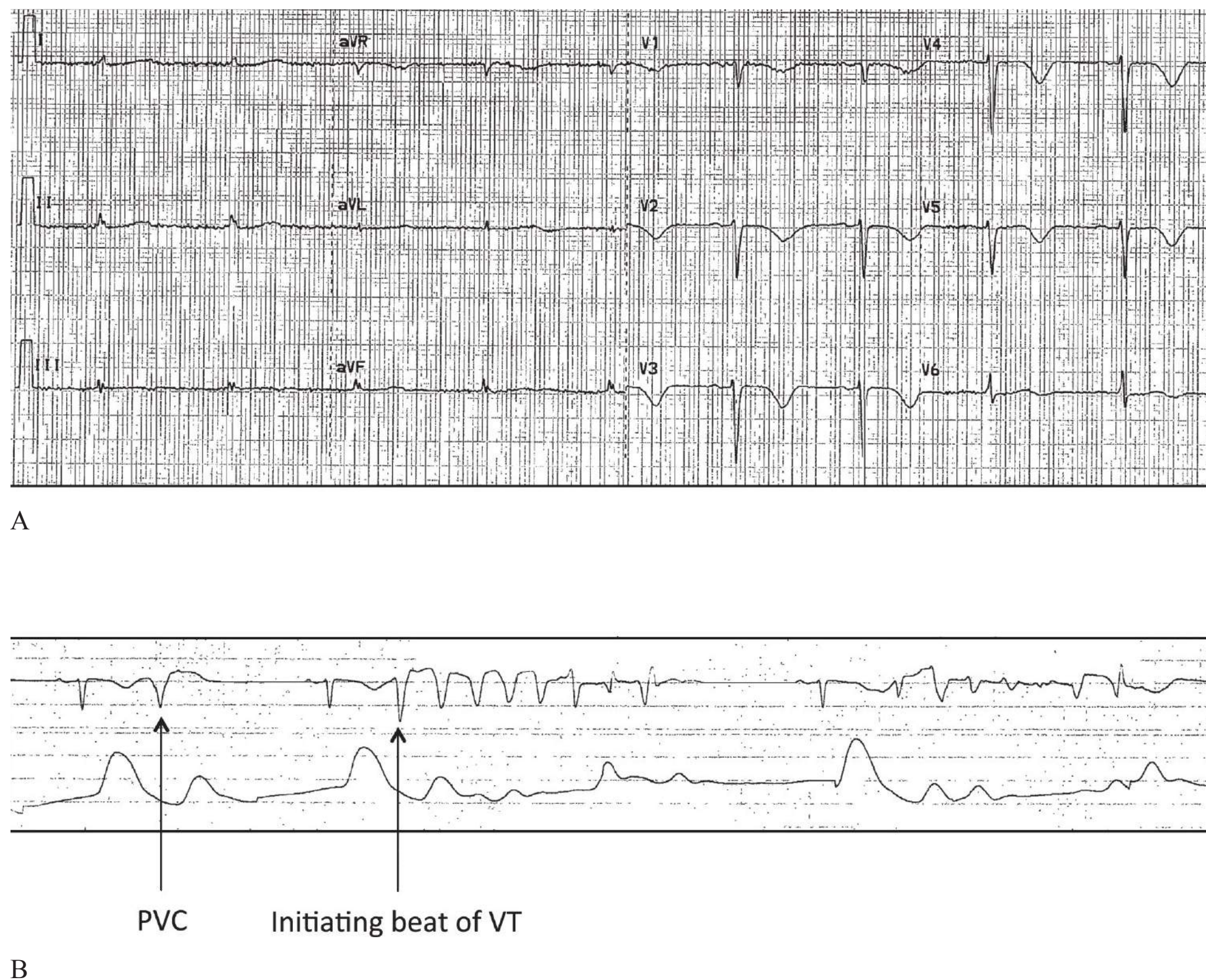


FIGURE 18-8

Electrocardiogram (ECG) of a patient with prolonged QT and episodes of torsade de pointes ventricular tachycardia (VT). A. Twelve-lead ECG showing a heart rate of 54, anterior wall T inversion, and QT interval of 600 ms. The corrected QT interval (QTc) is 585 ms. B. Telemetry ECG tracing with digital

pulse waveform demonstrating bursts of torsade de pointes VT. The initiating sequence of the VT is characteristic, with a PVC inducing a pause followed by a sinus beat that had a longer QT and interruption of the T wave by a PVC that is the first beat of VT. The VT is self-terminating in this case.

to suppress PVCs, usually suppresses VT recurrences. These maneuvers allow time for correction of associated electrolyte disturbance (hypokalemia and hypocalcemia) and bradycardia and removal of any causative drugs (Table 18-3). Drug interactions that elevate levels of the offending agent are often a precipitating factor. Patients who experience a polymorphic VT induced by QT prolongation should be considered to have a susceptibility to the arrhythmia and should avoid all future exposure to medications known to prolong the QT interval.

Congenital long QT syndrome

The congenital long QT syndrome (LQTS) is caused by mutations in genes coding for cardiac ion channels responsible for ventricular repolarization. The corrected QT (QTc) is typically prolonged to greater than 440 ms in men and 460 ms in women. Symptoms are due to Torsade de Pointes VT (Fig. 18-8). Several forms of congenital LQTS have been identified, but three groups of mutations that lead to LQTS type 1 (LQTS-1), LQTS type 2 (LQTS-2), or LQTS type 3 (LQTS-3) account for 90% of cases. The most frequently encountered mutations, LQTS1 and LQTS2, are due to abnormalities of potassium channels, but mutations affecting the sodium

channel (LQTS3) and calcium channels have also been described (Table 18-3).

Patients often present with syncope or cardiac arrest, usually during childhood. In LQTS-1, episodes tend to occur during exertion, particularly swimming. In LQTS-2, sudden auditory stimuli or emotional upset predispose to events. In LQTS-3, sudden death during sleep is a notable feature. Asymptomatic patients may be discovered in the course of family screening or on a routine ECG. Genotyping can be helpful for family screening and to provide reassurance regarding the diagnosis. Correlations of genotype with risk and response to therapy are beginning to emerge. In most patients with LQTS-1 or LQTS-2, adequate doses of beta blocker therapy (the nonselective agents nadolol or propranolol) are sufficient protection from arrhythmia episodes. Markers of increased risk include QTc interval exceeding 0.5 s, female gender, and a history of syncope or cardiac arrest. Recurrent syncope despite beta blocker therapy or a high-risk profile merits consideration of an ICD. Avoidance of QT-prolonging drugs is critical for all patients with LQTS, including those who are genotype positive but have normal QT intervals.

Short QT syndrome

Short QT syndrome is very rare compared to LQTS. The QTc is shorter than 0.36 s, and usually less than 0.3 s. The genetic abnormality causes a gain of function of the potassium channel (I_{Kr}) or reduced inward depolarizing currents. The abnormality is associated with atrial fibrillation, polymorphic VT, and sudden death.

Brugada syndrome

Brugada syndrome is a rare syndrome characterized by >0.2 mV of ST-segment elevation with a coved ST segment and negative T wave in more than one anterior precordial lead (V_1 – V_3) (Fig. 18-6) and episodes of syncope or cardiac arrest due to polymorphic VT in the absence of structural heart disease. Cardiac arrest may occur during sleep or be provoked by febrile illness. Males are more commonly affected than females. Mutations involving cardiac sodium channels are identified in approximately 25% of cases. Distinction from patients with similar ST elevation owing to LV hypertrophy, pericarditis, myocardial ischemia or MI hyperkalemia, hypothermia, right bundle branch block, and ARVC is often difficult. Furthermore, the characteristic ST-segment elevation can wax and wane over time and may become pronounced during acute illness and fever. Administration of the sodium channel blocking drug flecainide, ajmaline, or procainamide can augment or unmask ST elevation in affected individuals. An ICD is indicated for individuals who have had unexplained syncope or been resuscitated from cardiac arrest. Quinidine has been used successfully to suppress frequent episodes of VT.

Early repolarization syndrome

Patients resuscitated from VF who have no structural heart disease or other identified abnormality have a higher prevalence of J-point elevation with notching in the terminal QRS. A family history of sudden death is present in some patients, suggesting a potential genetic basis. J-point elevation is also seen in some patients with the Brugada syndrome and associated with a higher risk of arrhythmias. An ICD is recommended for those who have had prior cardiac arrest. It should be noted that J-point elevation is commonly seen as a normal variant, and in the absence of specific symptoms, the clinical relevance is not known.

Catecholaminergic polymorphic VT

This rare familial syndrome is due to mutations in the cardiac ryanodine receptor and, less commonly, the sarcoplasmic calcium binding protein, calsequestrin 2. These mutations result in abnormal sarcoplasmic calcium handling and polymorphic ventricular arrhythmias that resemble those seen with digitalis toxicity. The VT is polymorphic or has a characteristic alternating QRS morphology termed bidirectional VT. Patients usually present during childhood with exercise- or emotion-induced palpitations, syncope, or cardiac

arrest. β -Adrenergic blockers (e.g., nadolol and propranolol) and an ICD are recommended. Verapamil, flecainide, or surgical left cardiac sympathetic denervation reduces or prevents recurrent VT in some patients.

Hypertrophic cardiomyopathy (HCM)

HCM is the most common genetic cardiovascular disorder, occurring in 1 in 500 individuals, and is a prominent cause of sudden death before the age of 35 years (**Chap. 27**). Sudden death can be due to polymorphic VT/VF. Rarely, sustained monomorphic VT occurs related to areas of ventricular scar. Risk factors include young age, nonsustained VT, failure of blood pressure to increase during exercise, recent (within 6 months) syncope, ventricular wall thickness >3 cm, and possibly the severity of LV outflow obstruction. An ICD is generally indicated for high-risk patients, but the specific risk profile warranting an ICD continues to be debated. Surgical myectomy, performed to relieve outflow obstruction, has been associated with a sudden death rate of less than 1% per year. The reported annual rate of sustained VT or sudden death after transcatheter ethanol septal ablation done to relieve outflow obstruction has been reported to range between 1 and 5%.

Genetic dilated cardiomyopathies

Genetic dilated cardiomyopathies account for 30–40% of cases of nonischemic dilated cardiomyopathies. Some are associated with muscular dystrophy. Autosomal dominant, recessive, X-linked, and mitochondrial inheritance patterns are recognized. Mutations in genes coding for structural proteins of the nuclear lamina (lamin A and C) and the SCN5A gene are particularly associated with conduction system disease and ventricular arrhythmias. Patients can experience polymorphic VT and cardiac arrest or develop areas of scar causing sustained monomorphic VT. ICDs are recommended for those who have had a sustained VT or are at high risk due to significantly depressed ventricular function (LV ejection fraction of ≤ 0.35 and associated with heart failure) or a malignant family history of sudden death.

Ventricular fibrillation

VF is characterized by disordered electrical ventricular activation without identifiable QRS complexes (Fig. 18-3E). Spiral wave reentry and multiple circulating reentry wavefronts are possible mechanisms. Sustained polymorphic or monomorphic VT that degenerates to VF is a common cause of out-of-hospital cardiac arrest. Treatment follows ACLS guidelines with defibrillation to restore sinus rhythm. If resuscitation is successful, further evaluation is performed to identify and treat underlying heart disease and potential causes of the arrhythmia, including the possibility that monomorphic or polymorphic VT could have initiated VF. If a transient reversible cause such as acute MI is not

210 identified, therapy to reduce the risk of sudden death with an ICD is often warranted. Chronic amiodarone therapy may be considered for individuals who are not ICD candidates.

Incessant VT and electrical storm

VT is incessant when it continues to recur shortly after electrical, pharmacologic, or spontaneous conversion to sinus rhythm. “VT storm” or “electrical storm” refers to three or more separate episodes of VT within 24 h, most commonly encountered in patients with ICDs. Slow incessant VT is sometimes asymptomatic, but can cause heart failure or tachycardia-induced cardiomyopathy. More commonly, these presentations are life-threatening and require emergent therapy. Measures to reduce sympathetic tone, including β -adrenergic blockade, sedation, and general anesthesia, have been used effectively. Intravenous administration of amiodarone and lidocaine can be effective for suppression. Urgent catheter ablation can be lifesaving.

TREATMENT Ventricular Arrhythmias

ANTIARRHYTHMIC DRUGS Use of antiarrhythmic drugs is based on consideration of the risks and potential benefit for the individual patient. The potential to increase the frequency of VT or cause a new VT, an undesirable effect known as “proarrhythmia,” is a potential risk. Many drugs have multiple effects, often blocking more than one channel. **Drug doses, metabolism, and adverse effects are summarized in Chap. 18.**

β -Adrenergic Blockers Many ventricular arrhythmias are sensitive to sympathetic stimulation, and β -adrenergic stimulation also diminishes the electrophysiologic effects of many antiarrhythmic drugs. The safety of β -blocking agents makes them the first choice of therapy for most ventricular arrhythmias. They are particularly useful for exercise-induced arrhythmias and idiopathic arrhythmias, but have limited efficacy for most arrhythmias associated with heart disease. Bradyarrhythmias are the major cardiac toxicity.

Calcium Channel Blockers The nondihydropyridine calcium channel blockers diltiazem and verapamil can be effective for some idiopathic VTs. The risk of proarrhythmia is low, but they have negative inotropic and vasodilatory effects that can aggravate hypotension.

Sodium Channel-Blocking Agents Drugs whose major effect is mediated through sodium channel blockade include mexiletine, quinidine, disopyramide, flecainide, and propafenone, which are available for chronic oral therapy (Table 18-3). Lidocaine, quinidine, and procainamide are available as intravenous formulations. Quinidine, disopyramide, and procainamide also have potassium channel-blocking effects that prolong the QT interval. These agents have potential proar-

rhythmic effects and, with the possible exception of quinidine, also have negative inotropic effects that may contribute to increased mortality observed in patients with prior MI. Long-term therapy is generally avoided in patients with structural heart disease but may be used to reduce symptomatic arrhythmias in patients with ICDs.

Potassium Channel-Blocking Agents Sotalol and dofetilide block the delayed rectifier potassium channel I_{Kr} , thereby prolonging the QT interval. Sotalol also has nonselective β -adrenergic blocking activity. It has a modest effect on reducing ICD shocks due to ventricular and atrial arrhythmias. Proarrhythmia with Torsade de Pointes due to QT prolongation occurs in 3–5% of patients. Both sotalol and dofetilide are excreted via the kidneys, necessitating dose adjustment or avoidance in renal insufficiency. These drugs must be avoided in patients with other risk factors for Torsade de Pointes, including QT prolongation, hypokalemia, and significant bradycardia.

Amiodarone and Dronedarone Amiodarone, which blocks multiple cardiac ionic currents and has sympatholytic activity, suppresses a variety of ventricular arrhythmias. It is administered intravenously for life-threatening arrhythmias. During chronic oral therapy, electrophysiologic effects develop over several days. It is more effective than sotalol in reducing ICD shocks and is the preferred drug for ventricular arrhythmias in patients with heart disease who are not candidates for an ICD. Bradyarrhythmias are the major cardiac adverse effect. Ventricular proarrhythmia can occur, but Torsade de Pointes VT is rare. Noncardiac toxicities are a major problem and contribute to drug discontinuation in approximately a third of patients during long-term therapy. Pneumonitis or pulmonary fibrosis occurs in approximately 1% of patients. Photosensitivity is common, and neuropathy and ocular toxicity can occur. Systematic monitoring is recommended during chronic therapy, including assessment for thyroid and liver toxicity every 6 months and lung toxicity with a chest radiograph and/or determination of lung diffusing capacity annually. Dronedarone has structural similarities to amiodarone but without the iodine moiety. Efficacy for ventricular arrhythmias is poor, and it increases mortality in patients with heart failure.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS ICDs are highly effective for termination of VT and VF and also provide bradycardia pacing. ICDs decrease mortality in patients at risk for sudden death due to structural heart diseases. In all cases, ICDs are recommended only if there is also expectation for survival of at least a year with acceptable functional capacity. The exception is in cases of patients with end-stage heart disease who are awaiting cardiac transplantation outside the hospital, or who have left bundle branch block QRS prolongation such that they are likely to have improvement in ventricular function with cardiac resynchronization therapy from a biventricular ICD.

ICDs can often terminate monomorphic VT by a burst of rapid pacing faster than the VT, known as antitachycardia

pacing (ATP) (**Fig. 18-9A**). If ATP fails or is not a programmed treatment, as is often the case for rapid VT or VF, a shock is delivered (Fig. 18-9B). Shocks are painful if the patient is conscious. The most common ICD complication is the delivery of unnecessary therapy (either ATP or shocks) in response to a rapid supraventricular tachycardia or electrical noise as a result of an ICD lead fracture. Interrogation of the ICD, which can be performed remotely and communicated via Internet, is critical after an ICD shock to determine the arrhythmia diagnosis and exclude an unnecessary therapy. Device infection occurs in approximately 1% of patients.

Despite prompt termination of VT or VF by an ICD, the occurrence of these arrhythmias predicts subsequent increased mortality and risk of heart failure. Occurrence of VT or VF should therefore prompt assessment for potential causes including worsening heart failure, electrolyte abnormalities, and ischemia. Repeated shocks, even if appropriate, often induce posttraumatic stress disorder. Antiarrhythmic drugs mostly in the form of amiodarone or catheter ablation are often required for suppression of recurrent arrhythmias. Antiarrhythmic drug therapy can alter the VT rate and the energy required for defibrillation, thereby necessitating programming changes in the ICD's algorithms for detection and therapy.

CATHETER ABLATION FOR VT Catheter ablation is performed by guiding an electrode catheter to the arrhythmia origin and producing a thermal injury with radiofrequency current. The size and location of the arrhythmia substrate determine the ease and likely effectiveness of the procedure, as well as potential complications. The most common complications, which occur in <5% of patients, are related to vascular access, including bleeding, femoral hematomas, arteriovenous fistulae, and pseudoaneurysms.

Catheter ablation is a reasonable first-line therapy for many patients with symptomatic idiopathic VTs. Success rates for those originating from a focus in the right ventricular outflow tract are in the range of 80–90% but lower for idiopathic VTs arising in less common locations such as from the LV outflow tract or aortic root, along the atrioventricular valve annuli, and from the papillary muscles. Failure of ablation is often due to inability to induce the arrhythmia for precise localization or because the origin of the VT is from a site that is inaccessible or in close proximity to a coronary artery. Complications are infrequent but can include perforation with cardiac tamponade, atrioventricular block due to injury to the conduction system, and coronary artery injury for foci in proximity to a coronary vessel.

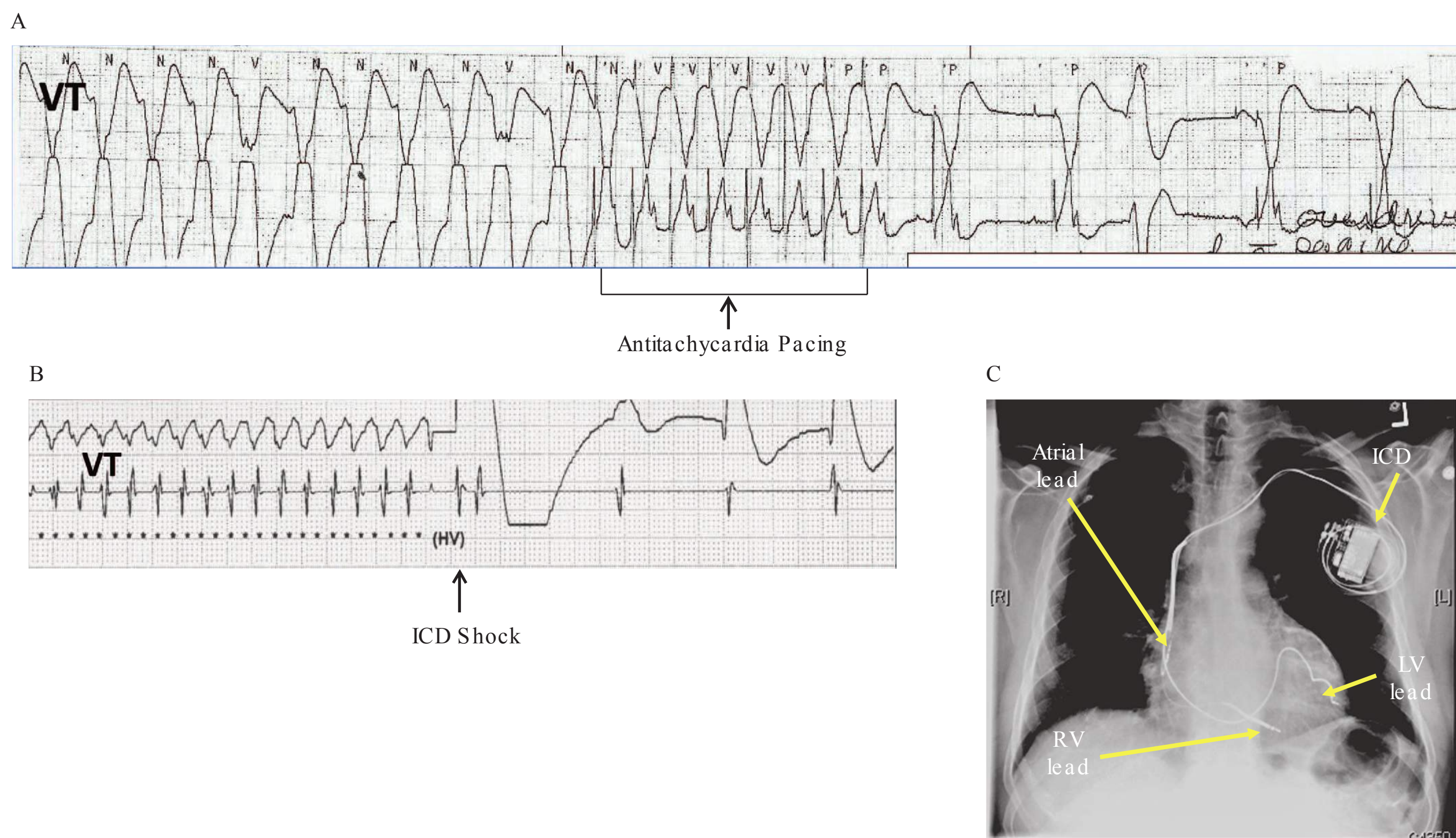


FIGURE 18-9

Implantable cardioverter-defibrillator (ICD) and therapies for ventricular arrhythmias. A. A monomorphic ventricular tachycardia (VT) is terminated by a burst of pacing impulses at a rate faster than VT (antitachycardia pacing). B. A rapid VT is converted with a high-voltage shock (arrow). The chest x-ray in

panel C shows the components of an ICD capable of biventricular pacing. ICD generator in the subcutaneous tissue of the left upper chest, pacing leads in the right atrium and the left ventricular (LV) branch of the coronary sinus (LV lead), and a pacing/defibrillating lead in the right ventricle (RV lead) are shown.

In patients with scar-related VT due to prior infarction or cardiomyopathy, ablation targets abnormal regions in the scar. Because these scars often contain multiple reentry circuits over relatively large regions, extensive areas of ablation are required, and these areas are often identified as regions of low voltage displayed on anatomic reconstructions of the ventricle (Fig. 18-5). If the circuits are not confined to the subendocardial scar, epicardial mapping and ablation can be performed via a subxiphoid pericardial puncture, similar to a pericardiocentesis. Epicardial mapping and ablation are often required for VTs due to nonischemic cardiomyopathy, but also have potentially greater risks of bleeding, coronary injury, and postprocedure pericarditis, which is usually transient. For drug-refractory VT due to prior MI, ablation abolishes VT in approximately half of patients and reduces the frequency of VT in an additional 20%. More than one procedure is necessary in up to 30% of patients. Ablation can be lifesaving for patients with very frequent or incessant VT. Procedure-related mortality is in the range of 3%, with most mortality due to continued uncontrollable VT when the procedure fails. In nonischemic heart disease, the arrhythmia substrate locations are more variable and outcomes are less well defined.

Catheter ablation can also be lifesaving for rare patients with recurrent polymorphic VT and VF that is repeatedly initiated by a uniform PVC. The initiating ectopic beat often originates from the Purkinje system or the right ventricular outflow tract and can be targeted for ablation.

When antiarrhythmic drug therapy and catheter ablation fail or are not options, surgical cryoablation, often combined with aneurysmectomy, can be effective therapy for recurrent VT due to prior MI and has also been used successfully in a few patients with nonischemic heart disease. Few centers

now maintain the expertise for this therapy. Injection of absolute ethanol into the coronary arterial blood supply of the arrhythmia substrate has also been used for ablation in a small number of patients who have failed catheter ablation and drugs.

SUMMARY

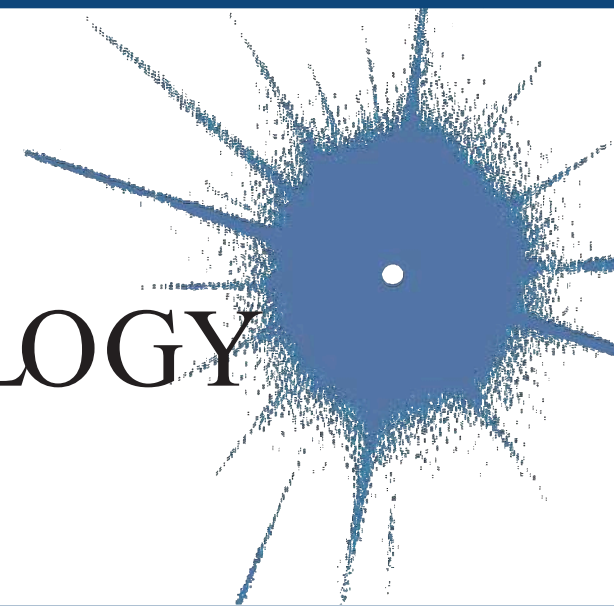
Patients with ventricular arrhythmias fall into three general groups. The first are those who have associated structural heart disease that must be detected. The risk of life-threatening arrhythmias causing sudden death is indicated by the nature of the arrhythmia—sustained (or causing cardiac arrest) or nonsustained, in which case the risk of life-threatening arrhythmias is assessed from the severity of the heart disease, usually the severity of ventricular dysfunction. ICDs provide the most protection from sudden arrhythmic death. The second group comprises those who do not have recognizable structural heart disease, but have a genetic syndrome associated with increased risk of sudden death. A family history of sudden death and abnormal electrocardiogram most frequently suggest the diagnosis. The third group includes individuals with benign idiopathic arrhythmias who may require therapy to control symptoms, but who are not at significant risk for life-threatening arrhythmias. The appropriate recognition of these patients is facilitated by thoughtful application of ECG and cardiac imaging. High-risk individuals benefit from specialized care for consideration of ICDs, catheter ablation, and antiarrhythmic drug therapy.

SECTION IV

DISORDERS OF THE HEART

CHAPTER 19

HEART FAILURE: PATHOPHYSIOLOGY AND DIAGNOSIS



Douglas L. Mann ■ Murali Chakinala

HEART FAILURE

DEFINITION

Despite repeated attempts to develop a mechanistic definition that encompasses the heterogeneity and complexity of heart failure (HF), no single conceptual paradigm has withstood the test of time. The current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines define HF as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to the cardinal clinical symptoms of dyspnea and fatigue and signs of HF, namely edema and rales. Because many patients present without signs or symptoms of volume overload, the term “heart failure” is preferred over the older term “congestive heart failure.”

EPIDEMIOLOGY



HF is a burgeoning problem worldwide, with more than 20 million people affected. The overall prevalence of HF in the adult population in developed countries is 2%. HF prevalence follows an exponential pattern, rising with age, and affects 6–10% of people over age 65. Although the relative incidence of HF is lower in women than in men, women constitute at least one-half the cases of HF because of their longer life expectancy. In North America and Europe, the lifetime risk of developing HF is approximately one in five for a 40-year-old. The overall prevalence of HF is thought to be increasing, in part because current therapies for cardiac disorders, such as myocardial infarction (MI), valvular heart disease, and arrhythmias, are allowing patients to survive longer. Very little is known about the prevalence or risk of developing HF in emerging nations because of the lack of population-based studies

in those countries. HF was once thought to arise primarily in the setting of a depressed left ventricular (LV) ejection fraction (EF); however, epidemiologic studies have shown that approximately one-half of patients who develop HF have a normal or preserved EF ($EF \geq 50\%$). Accordingly, the historical terms “systolic” and “diastolic” HF have been abandoned, and HF patients are now broadly categorized into HF with a reduced EF (HFrEF; formerly systolic failure) or HF with a preserved EF (HFpEF; formerly diastolic failure).

ETIOLOGY

As shown in **Table 19-1**, any condition that leads to an alteration in LV structure or function can predispose a patient to developing HF. Although the etiology of HF in patients with a preserved EF differs from that of patients with depressed EF, there is considerable overlap between the etiologies of these two conditions. In industrialized countries, coronary artery disease (CAD) has become the predominant cause in men and women and is responsible for 60–75% of cases of HF. Hypertension contributes to the development of HF in 75% of patients, including most patients with CAD. Both CAD and hypertension interact to augment the risk of HF, as does diabetes mellitus.

In 20–30% of the cases of HF with a depressed EF, the exact etiologic basis is not known. These patients are referred to as having nonischemic, dilated, or idiopathic cardiomyopathy if the cause is unknown (**Chap. 27**). Prior viral infection or toxin exposure (e.g., alcoholic or chemotherapeutic) also may lead to a dilated cardiomyopathy. Moreover, it is becoming increasingly clear that a large number of cases of dilated cardiomyopathy are secondary to specific genetic defects, most notably those in the cytoskeleton. Most forms of familial dilated cardiomyopathy are inherited in an autosomal

TABLE 19-1

ETIOLOGIES OF HEART FAILURE	
Depressed Ejection Fraction (<40%)	
Coronary artery disease	Nonischemic dilated
Myocardial infarction ^a	cardiomyopathy
Myocardial ischemia ^a	Familial/genetic disorders
Chronic pressure overload	Infiltrative disorders ^a
Hypertension ^a	Toxic/drug-induced damage
Obstructive valvular disease ^a	Metabolic disorder ^a
Chronic volume overload	Viral
Regurgitant valvular disease	Chagas' disease
Intracardiac (left-to-right)	Disorders of rate and
shunting	rhythm
Extracardiac shunting	Chronic bradyarrhythmias
Chronic lung disease	Chronic tachyarrhythmias
Cor pulmonale	
Pulmonary vascular disorders	
Preserved Ejection Fraction (>40–50%)	
Pathologic hypertrophy	Restrictive cardiomyopathy
Primary (hypertrophic	Infiltrative disorders (amy-
cardiomyopathies)	loidosis, sarcoidosis)
Secondary (hypertension)	Storage diseases
Aging	(hemochromatosis)
	Fibrosis
	Endomyocardial disorders
High-Output States	
Metabolic disorders	Excessive blood flow
Thyrotoxicosis	requirements
Nutritional disorders (beriberi)	Systemic arteriovenous
	shunting
	Chronic anemia

^aIndicates conditions that can also lead to heart failure with a preserved ejection fraction.

dominant fashion. Mutations of genes that encode cytoskeletal proteins (desmin, cardiac myosin, vinculin) and nuclear membrane proteins (laminin) have been identified thus far. Dilated cardiomyopathy also is associated with Duchenne's, Becker's, and limb-girdle muscular dystrophies. Conditions that lead to a high cardiac output (e.g., arteriovenous fistula, anemia) are seldom responsible for the development of HF in a normal heart; however, in the presence of underlying structural heart disease, these conditions can lead to overt HF.

GLOBAL CONSIDERATIONS



Rheumatic heart disease remains a major cause of HF in Africa and Asia, especially in the young. Hypertension is an important cause of HF in the African and African-American populations. Chagas' disease is still a major cause of HF in South America. Not surprisingly, anemia is a frequent comitant factor in HF in many developing nations. As developing nations undergo socioeconomic development, the epidemiology of HF is becoming similar to

that of Western Europe and North America, with CAD emerging as the single most common cause of HF. Although the contribution of diabetes mellitus to HF is not well understood, diabetes accelerates atherosclerosis and often is associated with hypertension.

PROGNOSIS

Despite many recent advances in the evaluation and management of HF, the development of symptomatic HF still carries a poor prognosis. Community-based studies indicate that 30–40% of patients die within 1 year of diagnosis and 60–70% die within 5 years, mainly from worsening HF or as a sudden event (probably because of a ventricular arrhythmia). Although it is difficult to predict prognosis in an individual, patients with symptoms at rest (New York Heart Association [NYHA] class IV) have a 30–70% annual mortality rate, whereas patients with symptoms with moderate activity (NYHA class II) have an annual mortality rate of 5–10%. Thus, functional status is an important predictor of patient outcome (Table 19-2).

TABLE 19-2

NEW YORK HEART ASSOCIATION CLASSIFICATION	
FUNCTIONAL CAPACITY	OBJECTIVE ASSESSMENT
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: Adapted from New York Heart Association, Inc., Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis, 6th ed. Boston, Little Brown, 1964, p. 114.

Figure 19-1 provides a general conceptual framework for considering the development and progression of HFrEF. As shown, HF may be viewed as a progressive disorder that is initiated after an index event either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or, alternatively, disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally. This index event may have an abrupt onset, as in the case of an MI; it may have a gradual or insidious onset, as in the case of hemodynamic pressure or volume overloading; or it may be hereditary, as in the case of many of the genetic cardiomyopathies. Regardless of the nature of the inciting event, the feature that is common to each of these index events is that they all in some manner produce a decline in the pumping capacity of the heart. In most instances, patients remain asymptomatic or minimally symptomatic after the initial decline in pumping capacity of the heart or develop symptoms only after the dysfunction has been present for some time.

Although the precise reasons why patients with LV dysfunction may remain asymptomatic is not certain, one potential explanation is that a number of compensatory mechanisms become activated in the presence of

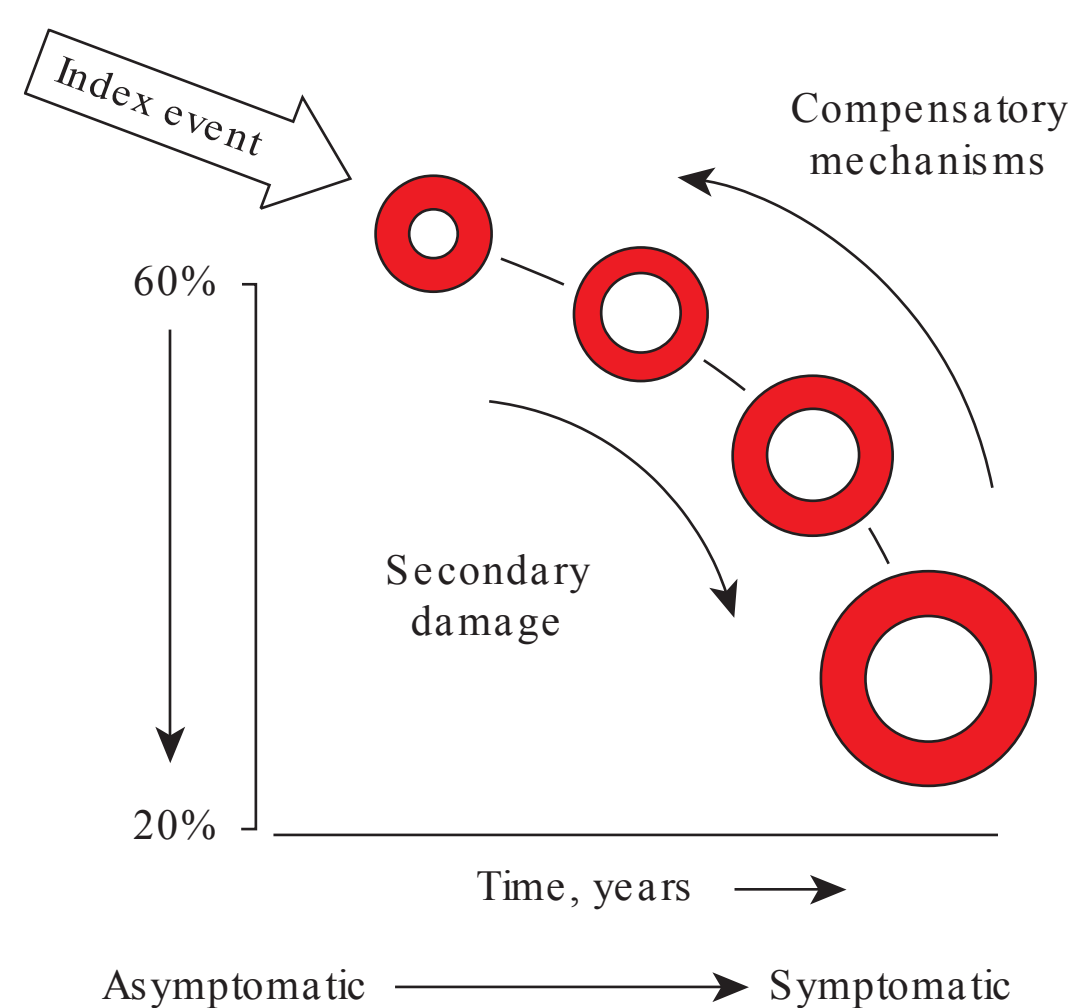


FIGURE 19-1

Pathogenesis of heart failure with a depressed ejection fraction. Heart failure begins after an index event produces an initial decline in the heart's pumping capacity. After this initial decline in pumping capacity, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin-aldosterone system, and the cytokine system. In the short term, these systems are able to restore cardiovascular function to a normal homeostatic range with the result that the patient remains asymptomatic. However, with time, the sustained activation of these systems can lead to secondary end-organ damage within the ventricle, with worsening left ventricular remodeling and subsequent cardiac decompensation. (From D Mann: *Circulation* 100:999, 1999.)

cardiac injury and/or LV dysfunction allowing patients to sustain and modulate LV function for a period of months to years. The compensatory mechanisms that have been described thus far include (1) activation of the renin-angiotensin-aldosterone (RAA) and adrenergic nervous systems, which are responsible, respectively, for maintaining cardiac output through increased retention of salt and water (**Fig. 19-2**), and (2) increased myocardial contractility. In addition, there is activation of a family of countervailing vasodilatory molecules, including the atrial and brain natriuretic peptides (ANP and BNP), prostaglandins (PGE₂ and PGI₂), and nitric oxide (NO), that offsets the excessive peripheral vascular vasoconstriction. Genetic background, sex, age, or environment may influence these compensatory mechanisms, which are able to modulate LV function within a physiologic/homeostatic range so that the functional capacity of the patient is preserved or is depressed only minimally. Thus, patients may remain asymptomatic or minimally symptomatic for a period of years; however, at some point patients become overtly symptomatic, with a resultant striking increase in morbidity and mortality rates. Although the exact mechanisms that are responsible for this transition are not known, as will be discussed below, the transition to symptomatic HF is accompanied by increasing activation of neurohormonal, adrenergic, and cytokine systems that lead to a series of adaptive changes within the myocardium collectively referred to as LV remodeling.

In contrast to our understanding of the pathogenesis of HF with a depressed EF, our understanding of the mechanisms that contribute to the development of HF with a preserved EF is still evolving. That is, although diastolic dysfunction (see below) was thought to be the only mechanism responsible for the development of HF with a preserved EF, community-based studies suggest that additional extracardiac mechanisms may be important, such as increased vascular stiffness and impaired renal function.

BASIC MECHANISMS OF HEART FAILURE

Heart failure with a reduced ejection fraction

LV remodeling develops in response to a series of complex events that occur at the cellular and molecular levels (**Table 19-3**). These changes include (1) myocyte hypertrophy; (2) alterations in the contractile properties of the myocyte; (3) progressive loss of myocytes through necrosis, apoptosis, and autophagic cell death; (4) β -adrenergic desensitization; (5) abnormal myocardial energetics and metabolism; and (6) reorganization of the extracellular matrix with dissolution of the organized structural collagen weave surrounding myocytes and subsequent replacement by an interstitial collagen matrix that does not provide structural support to

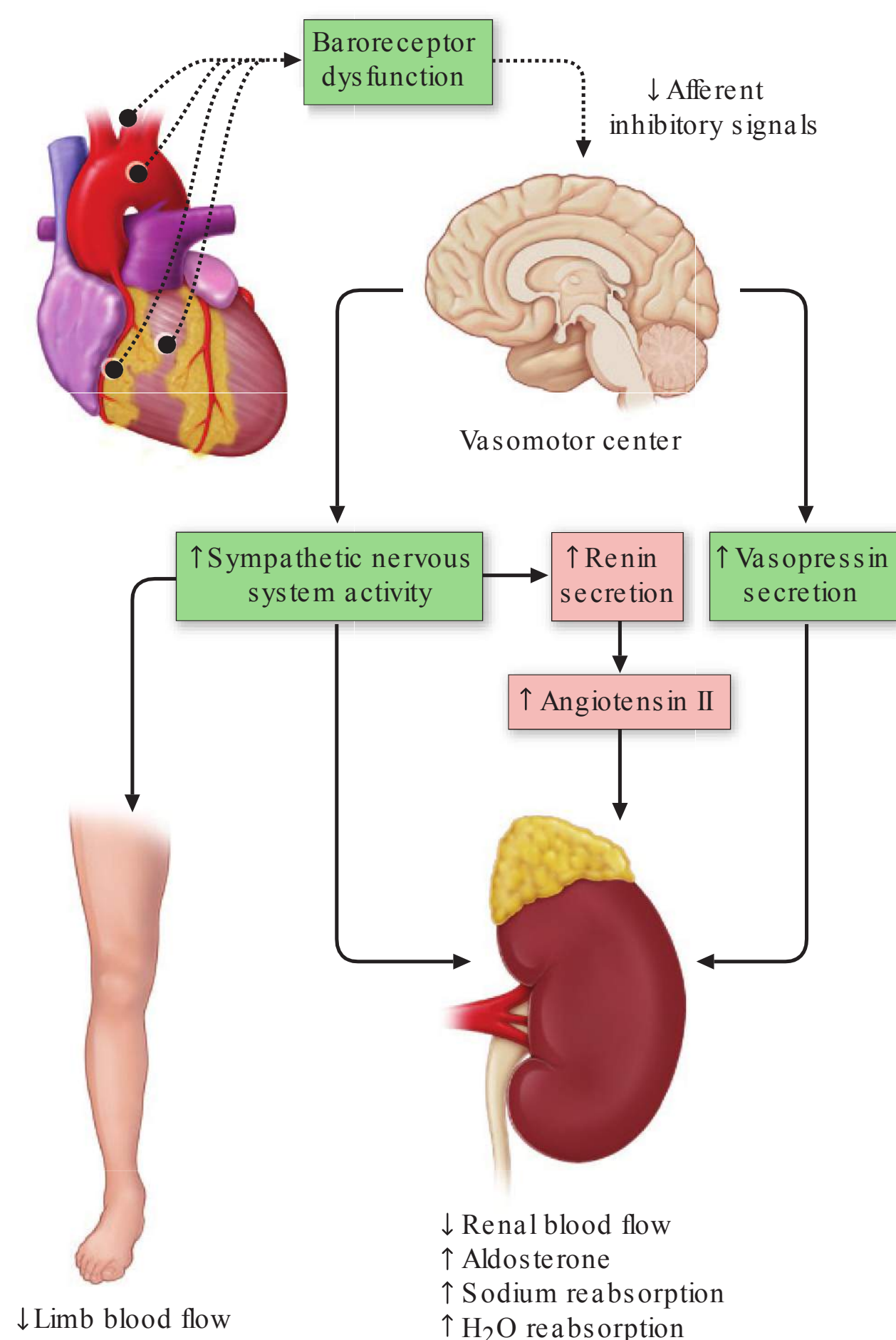


FIGURE 19-2

Activation of neurohormonal systems in heart failure. The decreased cardiac output in heart failure (HF) patients results in an “unloading” of high-pressure baroreceptors (circles) in the left ventricle, carotid sinus, and aortic arch. This unloading of the peripheral baroreceptors leads to a loss of inhibitory parasympathetic tone to the central nervous system (CNS), with a resultant generalized increase in efferent sympathetic tone, and nonosmotic release of arginine vasopressin (AVP) from the pituitary. AVP (or antidiuretic hormone [ADH]) is a powerful vasoconstrictor that increases the permeability of the renal collecting ducts, leading to the reabsorption of free water. These afferent signals to the CNS also activate efferent sympathetic nervous system pathways that innervate the heart, kidney, peripheral vasculature, and skeletal muscles.

Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in the circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention and leads to vasoconstriction of the peripheral vasculature, myocyte hypertrophy, myocyte cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short-term adaptation by maintaining blood pressure, and hence perfusion to vital organs, the same neurohormonal mechanisms are believed to contribute to end-organ changes in the heart and the circulation and to the excessive salt and water retention in advanced HF. (Modified from A Nohria et al: Neurohormonal, renal and vascular adjustments, in *Atlas of Heart Failure: Cardiac Function and Dysfunction*, 5th ed, WSColucci [ed]. Philadelphia, Current Medicine Group 2008, pp. 89–117.)

TABLE 19-3

OVERVIEW OF LEFT VENTRICULAR REMODELING

Alterations in Myocyte Biology

Excitation-contraction coupling
Myosin heavy chain (fetal) gene expression
 β -Adrenergic desensitization
Hypertrophy
Myocytolysis
Cytoskeletal proteins

Myocardial Changes

Myocyte loss
Necrosis
Apoptosis
Autophagy
Alterations in extracellular matrix
Matrix degradation
Myocardial fibrosis

Alterations in Left Ventricular Chamber Geometry

Left ventricular (LV) dilation
Increased LV sphericity
LV wall thinning
Mitral valve incompetence

Source: Adapted from D. Mann: Pathophysiology of heart failure, in Braunwald's Heart Disease, 8th ed, PL Libby et al (eds). Philadelphia, Elsevier, 2008, p. 550.

the myocytes. The biologic stimuli for these profound changes include mechanical stretch of the myocyte, circulating neurohormones (e.g., norepinephrine, angiotensin II), inflammatory cytokines (e.g., tumor necrosis factor [TNF]), other peptides and growth factors (e.g., endothelin), and reactive oxygen species (e.g., superoxide). The sustained overexpression of these biologically active molecules is believed to contribute to the progression of HF by virtue of the deleterious effects they exert on the heart and the circulation. Indeed, this insight forms the clinical rationale for using pharmacologic agents that antagonize these systems (e.g., angiotensin-converting enzyme [ACE] inhibitors and beta blockers) in treating patients with HF (**Chap. 20**).

To understand how the changes that occur in the failing cardiac myocyte contribute to depressed LV systolic function in HF, it is instructive first to review the biology of the cardiac muscle cell (**Chap. 1**). Sustained neurohormonal activation and mechanical overload result in transcriptional and post-transcriptional changes in the genes and proteins that regulate excitation-contraction coupling and cross-bridge interaction (see **Figs. 1-6 and 1-7**). The changes that regulate excitation-contraction include decreased function of sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA2A), resulting in decreased calcium uptake into the sarcoplasmic reticulum (SR), and hyperphosphorylation of the ryanodine receptor, leading to calcium leakage

from the SR. The changes that occur in the cross-bridges include decreased expression of α -myosin heavy chain and increased expression of β -myosin heavy chain, myocytolysis, and disruption of the cytoskeletal links between the sarcomeres and the extracellular matrix. Collectively, these changes impair the ability of the myocyte to contract and therefore contribute to the depressed LV systolic function observed in patients with HF.

Myocardial relaxation is an adenosine triphosphate (ATP)-dependent process that is regulated by uptake of cytoplasmic calcium into the SR by SERCA2A and extrusion of calcium by sarcolemmal pumps (see Fig. 1-7). Accordingly, reductions in ATP concentration, as occurs in ischemia, may interfere with these processes and lead to slowed myocardial relaxation. Alternatively, if LV filling is delayed because LV compliance is reduced (e.g., from hypertrophy or fibrosis), LV filling pressures will similarly remain elevated at end diastole (see Fig. 1-11). An increase in heart rate disproportionately shortens the time for diastolic filling, which may lead to elevated LV filling pressures, particularly in noncompliant ventricles. Elevated LV end-diastolic filling pressures result in increases in pulmonary capillary pressures, which can contribute to the dyspnea experienced by patients with diastolic dysfunction. In addition to impaired myocardial relaxation, increased myocardial stiffness secondary to cardiac hypertrophy and increased myocardial collagen content may contribute to diastolic failure. Importantly, diastolic dysfunction can occur alone or in combination with systolic dysfunction in patients with HF.

Left ventricular remodeling

Ventricular remodeling refers to the changes in LV mass, volume, and shape and the composition of the heart that occur after cardiac injury and/or abnormal hemodynamic loading conditions. LV remodeling may contribute independently to the progression of HF by virtue of the mechanical burdens that are engendered by the changes in the geometry of the remodeled LV. In addition to the increase in LV end-diastolic volume, LV wall thinning occurs as the left ventricle begins to dilate. The increase in wall thinning, along with the increase in afterload created by LV dilation, leads to a functional afterload mismatch that may contribute further to a decrease in stroke volume. Moreover, the high end-diastolic wall stress might be expected to lead to (1) hypoperfusion of the subendocardium, with resultant worsening of LV function; (2) increased oxidative stress, with the resultant activation of families of genes that are sensitive to free radical generation (e.g., TNF and interleukin 1 β); and (3) sustained expression of stretch-activated genes (angiotensin II, endothelin, and TNF) and/or stretch activation of hypertrophic signaling pathways. Increasing LV dilation also results in tethering of

the papillary muscles with resulting incompetence of the mitral valve apparatus and functional mitral regurgitation, which in turn leads to further hemodynamic overloading of the ventricle. Taken together, the mechanical burdens that are engendered by LV remodeling contribute to the progression of HF. Recent studies have shown that LV remodeling can be reversed following medical and device therapy and that reverse LV remodeling is associated with improved clinical outcomes in patients with HFrEF. Indeed, one of the goals of therapy for HF is to prevent and/or reverse LV remodeling.

CLINICAL MANIFESTATIONS

Symptoms

The cardinal symptoms of HF are fatigue and shortness of breath. Although fatigue traditionally has been ascribed to the low cardiac output in HF, it is likely that skeletal-muscle abnormalities and other non-cardiac comorbidities (e.g., anemia) also contribute to this symptom. In the early stages of HF, dyspnea is observed only during exertion; however, as the disease progresses, dyspnea occurs with less strenuous activity, and it ultimately may occur even at rest. The origin of dyspnea in HF is probably multifactorial (Chap. 5). The most important mechanism is pulmonary congestion with accumulation of interstitial or intra-alveolar fluid, which activates juxta-capillary J receptors, which in turn stimulate the rapid, shallow breathing characteristic of cardiac dyspnea. Other factors that contribute to dyspnea on exertion include reductions in pulmonary compliance, increased airway resistance, respiratory muscle and/or diaphragm fatigue, and anemia. Dyspnea may become less frequent with the onset of right ventricular (RV) failure and tricuspid regurgitation.

Orthopnea

Orthopnea, which is defined as dyspnea occurring in the recumbent position, is usually a later manifestation of HF than is exertional dyspnea. It results from redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbency, with a resultant increase in pulmonary capillary pressure. Nocturnal cough is a common manifestation of this process and a frequently overlooked symptom of HF. Orthopnea generally is relieved by sitting upright or sleeping with additional pillows. Although orthopnea is a relatively specific symptom of HF, it may occur in patients with abdominal obesity or ascites and patients with pulmonary disease whose lung mechanics favor an upright posture.

Paroxysmal nocturnal dyspnea (PND)

This term refers to acute episodes of severe shortness of breath and coughing that generally occur at night and awaken the patient from sleep, usually 1–3 h after

the patient retires. PND may manifest as coughing or wheezing, possibly because of increased pressure in the bronchial arteries leading to airway compression, along with interstitial pulmonary edema that leads to increased airway resistance. Whereas orthopnea may be relieved by sitting upright at the side of the bed with the legs in a dependent position, patients with PND often have persistent coughing and wheezing even after they have assumed the upright position. Cardiac asthma is closely related to PND, is characterized by wheezing secondary to bronchospasm, and must be differentiated from primary asthma and pulmonary causes of wheezing.

Cheyne-stokes respiration

Also referred to as periodic respiration or cyclic respiration, Cheyne-Stokes respiration is present in 40% of patients with advanced HF and usually is associated with low cardiac output. Cheyne-Stokes respiration is caused by an increased sensitivity of the respiratory center to arterial P_{CO_2} . There is an apneic phase, during which arterial P_{O_2} falls and arterial P_{CO_2} rises. These changes in the arterial blood gas content stimulate the respiratory center, resulting in hyperventilation and hypocapnia, followed by recurrence of apnea. Cheyne-Stokes respirations may be perceived by the patient or the patient's family as severe dyspnea or as a transient cessation of breathing.

Acute pulmonary edema See Chap. 34

Other symptoms

Patients with HF also may present with gastrointestinal symptoms. Anorexia, nausea, and early satiety associated with abdominal pain and fullness are common complaints and may be related to edema of the bowel wall and/or a congested liver. Congestion of the liver and stretching of its capsule may lead to right upper-quadrant pain. Cerebral symptoms such as confusion, disorientation, and sleep and mood disturbances may be observed in patients with severe HF, particularly elderly patients with cerebral arteriosclerosis and reduced cerebral perfusion. Nocturia is common in HF and may contribute to insomnia.

PHYSICAL EXAMINATION

A careful physical examination is always warranted in the evaluation of patients with HF. The purpose of the examination is to help determine the cause of HF as well as to assess the severity of the syndrome. Obtaining additional information about the hemodynamic profile and the response to therapy and determining the prognosis are important additional goals of the physical examination.

General appearance and vital signs

In mild or moderately severe HF, the patient appears to be in no distress at rest except for feeling uncomfortable

when lying flat for more than a few minutes. In more severe HF, the patient must sit upright, may have labored breathing, and may not be able to finish a sentence because of shortness of breath. Systolic blood pressure may be normal or high in early HF, but it generally is reduced in advanced HF because of severe LV dysfunction. The pulse pressure may be diminished, reflecting a reduction in stroke volume. Sinus tachycardia is a nonspecific sign caused by increased adrenergic activity. Peripheral vasoconstriction leading to cool peripheral extremities and cyanosis of the lips and nail beds is also caused by excessive adrenergic activity.

Jugular veins

(See also Chap. 9) Examination of the jugular veins provides an estimation of right atrial pressure. The jugular venous pressure is best appreciated with the patient lying recumbent, with the head tilted at 45°. The jugular venous pressure should be quantified in centimeters of water (normal ≤ 8 cm) by estimating the height of the venous column of blood above the sternal angle in centimeters and then adding 5 cm. In the early stages of HF, the venous pressure may be normal at rest but may become abnormally elevated with sustained (~15 seconds) pressure on the abdomen (positive abdominojugular reflux). Giant v waves indicate the presence of tricuspid regurgitation.

Pulmonary examination

Pulmonary crackles (rales or crepitations) result from the transudation of fluid from the intravascular space into the alveoli. In patients with pulmonary edema, rales may be heard widely over both lung fields and may be accompanied by expiratory wheezing (cardiac asthma). When present in patients without concomitant lung disease, rales are specific for HF. Importantly, rales are frequently absent in patients with chronic HF, even when LV filling pressures are elevated, because of increased lymphatic drainage of alveolar fluid. Pleural effusions result from the elevation of pleural capillary pressure and the resulting transudation of fluid into the pleural cavities. Since the pleural veins drain into both the systemic and the pulmonary veins, pleural effusions occur most commonly with biventricular failure. Although pleural effusions are often bilateral in HF, when they are unilateral, they occur more frequently in the right pleural space.

Cardiac examination

Examination of the heart, although essential, frequently does not provide useful information about the severity of HF. If cardiomegaly is present, the point of maximal impulse (PMI) usually is displaced below the fifth

intercostal space and/or lateral to the midclavicular line, and the impulse is palpable over two interspaces. Severe LV hypertrophy leads to a sustained PMI. In some patients, a third heart sound (S_3) is audible and palpable at the apex. Patients with enlarged or hypertrophied right ventricles may have a sustained and prolonged left parasternal impulse extending throughout systole. An S_3 (or protodiastolic gallop) is most commonly present in patients with volume overload who have tachycardia and tachypnea, and it often signifies severe hemodynamic compromise. A fourth heart sound (S_4) is not a specific indicator of HF but is usually present in patients with diastolic dysfunction. The murmurs of mitral and tricuspid regurgitation are frequently present in patients with advanced HF.

Abdomen and extremities

Hepatomegaly is an important sign in patients with HF. When it is present, the enlarged liver is frequently tender and may pulsate during systole if tricuspid regurgitation is present. Ascites, a late sign, occurs as a consequence of increased pressure in the hepatic veins and the veins draining the peritoneum. Jaundice, also a late finding in HF, results from impairment of hepatic function secondary to hepatic congestion and hepatocellular hypoxemia and is associated with elevations of both direct and indirect bilirubin.

Peripheral edema is a cardinal manifestation of HF, but it is nonspecific and usually is absent in patients who have been treated adequately with diuretics. Peripheral edema is usually symmetric and dependent in HF and occurs predominantly in the ankles and the pretibial region in ambulatory patients. In bedridden patients, edema may be found in the sacral area (presacral edema) and the scrotum. Long-standing edema may be associated with indurated and pigmented skin.

Cardiac cachexia

With severe chronic HF, there may be marked weight loss and cachexia. Although the mechanism of cachexia is not entirely understood, it is probably multifactorial and includes elevation of the resting metabolic rate; anorexia, nausea, and vomiting due to congestive hepatomegaly and abdominal fullness; elevation of circulating concentrations of cytokines such as TNF; and impairment of intestinal absorption due to congestion of the intestinal veins. When present, cachexia augurs a poor overall prognosis.

DIAGNOSIS

The diagnosis of HF is relatively straightforward when the patient presents with classic signs and symptoms of

HF; however, the signs and symptoms of HF are neither specific nor sensitive. Accordingly, the key to making the diagnosis is to have a high index of suspicion, particularly for high-risk patients. When these patients present with signs or symptoms of HF, additional laboratory testing should be performed.

Routine laboratory testing

Patients with new-onset HF and those with chronic HF and acute decompensation should have a complete blood count, a panel of electrolytes, blood urea nitrogen, serum creatinine, hepatic enzymes, and a urinalysis. Selected patients should have assessment for diabetes mellitus (fasting serum glucose or oral glucose tolerance test), dyslipidemia (fasting lipid panel), and thyroid abnormalities (thyroid-stimulating hormone level).

Electrocardiogram (ECG)

A routine 12-lead ECG is recommended. The major importance of the ECG is to assess cardiac rhythm and determine the presence of LV hypertrophy or a prior MI (presence or absence of Q waves) as well as to determine QRS width to ascertain whether the patient may benefit from resynchronization therapy (see below). A normal ECG virtually excludes LV systolic dysfunction.

Chest x-ray

A chest x-ray provides useful information about cardiac size and shape, as well as the state of the pulmonary vasculature, and may identify noncardiac causes of the patient's symptoms. Although patients with acute HF have evidence of pulmonary hypertension, interstitial edema, and/or pulmonary edema, the majority of patients with chronic HF do not. The absence of these findings in patients with chronic HF reflects the increased capacity of the lymphatics to remove interstitial and/or pulmonary fluid.

Assessment of LV function

Noninvasive cardiac imaging (**Chap. 12**) is essential for the diagnosis, evaluation, and management of HF. The most useful test is the two-dimensional (2-D) echocardiogram/Doppler, which can provide a semiquantitative assessment of LV size and function as well as the presence or absence of valvular and/or regional wall motion abnormalities (indicative of a prior MI). The presence of left atrial dilation and LV hypertrophy, together with abnormalities of LV diastolic filling provided by pulse-wave and tissue Doppler, is useful for the assessment of HF with a preserved EF. The 2-D echocardiogram/Doppler is also invaluable in assessing RV size and pulmonary pressures, which are critical in the evaluation and

management of cor pulmonale (see below). Magnetic resonance imaging (MRI) also provides a comprehensive analysis of cardiac anatomy and function and is now the gold standard for assessing LV mass and volumes. MRI also is emerging as a useful and accurate imaging modality for evaluating patients with HF, both in terms of assessing LV structure and for determining the cause of HF (e.g., amyloidosis, ischemic cardiomyopathy, hemochromatosis).

The most useful index of LV function is the EF (stroke volume divided by end-diastolic volume). Because the EF is easy to measure by noninvasive testing and easy to conceptualize, it has gained wide acceptance among clinicians. Unfortunately, the EF has a number of limitations as a true measure of contractility, since it is influenced by alterations in afterload and/or preload. Nonetheless, with the exceptions indicated above, when the EF is normal ($\geq 50\%$), systolic function is usually adequate, and when the EF is significantly depressed ($<30\text{--}40\%$), contractility is usually depressed.

Biomarkers

Circulating levels of natriuretic peptides are useful and important adjunctive tools in the diagnosis of patients with HF. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), which are released from the failing heart, are relatively sensitive markers for the presence of HF with depressed EF; they also are elevated in HF patients with a preserved EF, albeit to a lesser degree. In ambulatory patients with dyspnea, the measurement of BNP or NT-proBNP is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty. Moreover, the measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF and can be useful to achieve optimal dosing of medical therapy in select clinically euvolemic patients. However, it is important to recognize that natriuretic peptide levels increase with age and renal impairment, are more elevated in women, and can be elevated in right HF from any cause. Levels can be falsely low in obese patients. Other biomarkers, such as soluble ST-2 and galectin-3, are newer biomarkers that can be used for determining the prognosis of HF patients.

Exercise testing

Treadmill or bicycle exercise testing is not routinely advocated for patients with HF, but either is useful for assessing the need for cardiac transplantation in patients with advanced HF (**Chap. 20**). A peak oxygen uptake (vo_2) <14 mL/kg per min is associated with a relatively poor prognosis. Patients with a $\text{vo}_2 <14$ mL/kg per min have been shown, in general, to have better survival when transplanted than when treated medically.

DIFFERENTIAL DIAGNOSIS

HF resembles but should be distinguished from (1) conditions in which there is circulatory congestion secondary to abnormal salt and water retention but in which there is no disturbance of cardiac structure or function (e.g., renal failure), and (2) noncardiac causes of pulmonary edema (e.g., acute respiratory distress syndrome). In most patients who present with classic signs and symptoms of HF, the diagnosis is relatively straightforward. However, even experienced clinicians have difficulty differentiating the dyspnea that arises from cardiac and pulmonary causes (**Chap. 5**). In this regard, noninvasive cardiac imaging, biomarkers, pulmonary function testing, and chest x-ray may be useful. A very low BNP or NT-proBNP may be helpful in excluding a cardiac cause of dyspnea in this setting. Ankle edema may arise secondary to varicose veins, obesity, renal disease, or gravitational effects. When HF develops in patients with a preserved EF, it may be difficult to determine the relative contribution of HF to the dyspnea that occurs in chronic lung disease and/or obesity.

COR PULMONALE

DEFINITION

Cor pulmonale, often referred to as pulmonary heart disease, can be defined as altered RV structure and/or function in the context of chronic lung disease and is triggered by the onset of pulmonary hypertension. Although RV dysfunction is also an important sequela of HFpEF and HFrEF, this is not considered as cor pulmonale.

ETIOLOGY AND EPIDEMIOLOGY

Cor pulmonale develops in response to acute or chronic changes in the pulmonary vasculature and/or the lung parenchyma that are sufficient to cause pulmonary hypertension. The true prevalence of cor pulmonale is difficult to ascertain. First, not all patients with chronic lung disease will develop cor pulmonale, which may be subclinical in compensated individuals. Second, our ability to diagnose pulmonary hypertension and cor pulmonale by routine physical examination and laboratory testing is relatively insensitive. However, advances in 2-D echo/Doppler imaging and biomarkers (BNP) can make it easier to identify cor pulmonale.

Once patients with chronic pulmonary or pulmonary vascular disease develop cor pulmonale, the prognosis worsens. Although chronic obstructive pulmonary disease (COPD) and chronic bronchitis are responsible for approximately 50% of the cases of cor pulmonale in North America, any disease that affects the pulmonary

222 vasculature (**Chap. 49**) or parenchyma can lead to cor pulmonale (**Table 19-4**). Primary pulmonary vascular disorders are relatively rare causes of cor pulmonale, but cor pulmonale is extremely common with these conditions, given the magnitude of pulmonary hypertension present.

PATHOPHYSIOLOGY AND BASIC MECHANISMS

Although many conditions can lead to cor pulmonale, the common pathophysiologic mechanism is pulmonary hypertension that is sufficient to alter RV structure (i.e., dilation with or without hypertrophy) and function. Normally, pulmonary artery pressures are only ~15 mmHg and do not increase even with multiples of resting cardiac output, because of vasodilation and blood vessel recruitment of the pulmonary circulatory bed. But, in the setting of parenchymal lung diseases, primary pulmonary vascular disorders, or chronic (alveolar) hypoxia, the circulatory bed undergoes varying degrees of vascular remodeling, vasoconstriction, and destruction. As a result, pulmonary artery pressures and RV afterload increase, setting the stage for cor

pulmonale (Table 19-4). The systemic consequences of cor pulmonale relate to alterations in cardiac output as well as salt and water homeostasis. Anatomically, the RV is a thin-walled, compliant chamber that is better suited to handle volume overload than pressure overload. Thus, the sustained pressure overload imposed by pulmonary hypertension and increased pulmonary vascular resistance eventually causes the RV to fail.

The response of the RV to pulmonary hypertension depends on the acuteness and severity of the pressure overload. Acute cor pulmonale occurs after a sudden and severe stimulus (e.g., massive pulmonary embolus), with RV dilatation and failure but no RV hypertrophy (**Chap. 45**). Chronic cor pulmonale, however, is associated with a more slowly evolving and progressive pulmonary hypertension that leads to initial modest RV hypertrophy and subsequent RV dilation. Acute decompensation of previously compensated chronic cor pulmonale is a common clinical occurrence. Triggers include worsening hypoxia from any cause (e.g., pneumonia), acidemia (e.g., exacerbation of COPD), acute pulmonary embolus, atrial tachyarrhythmia, hypervolemia, and mechanical ventilation that leads to compressive forces on alveolar blood vessels.

CLINICAL MANIFESTATIONS

Symptoms

The symptoms of chronic cor pulmonale generally are related to the underlying pulmonary disorder. Dyspnea, the most common symptom, is usually the result of the increased work of breathing secondary to changes in elastic recoil of the lung (fibrosing lung diseases), altered respiratory mechanics (e.g., overinflation with COPD), or inefficient ventilation (e.g., primary pulmonary vascular disease). Orthopnea and PND are rarely symptoms of isolated right HF and usually point toward concurrent left heart dysfunction. Rarely, these symptoms reflect increased work of breathing in the supine position resulting from compromised diaphragmatic excursion. Abdominal pain and ascites that occur with cor pulmonale are similar to the right HF that ensues in chronic HF. Lower-extremity edema may occur secondary to neurohormonal activation, elevated RV filling pressures, or increased levels of carbon dioxide and hypoxemia, which can lead to peripheral vasodilation and edema formation.

Signs

Many of the signs encountered in cor pulmonale are also present in HF patients with a depressed EF, including tachypnea, elevated jugular venous pressures, hepatomegaly, and lower-extremity edema. Patients may have prominent v waves in the jugular venous pulse as a result of tricuspid regurgitation. Other cardiovascular signs include an RV heave palpable along the left sternal

TABLE 19-4

ETIOLOGY OF CHRONIC COR PULMONALE
Diseases of the Lung Parenchyma
Chronic obstructive pulmonary disease
Emphysema
Chronic bronchitis
Cystic fibrosis
Idiopathic interstitial pneumonitis
Idiopathic pulmonary fibrosis
Nonspecific interstitial pneumonitis
Sarcoidosis
Bronchiectasis
Pulmonary Langerhans cell histiocytosis
Lymphangioleiomyomatosis
Disorders of Chronic (Alveolar) Hypoxia
Alveolar hypoventilation syndromes
Obesity hypoventilation syndrome
Central hypoventilation syndrome
Neuromuscular respiratory failure
Chest wall disorders
Kyphoscoliosis
Living at high altitude
Diseases of the Pulmonary Vasculature
Pulmonary arterial hypertension (PAH)
Idiopathic PAH
Heritable PAH
Associated PAH
Venoocclusive disease
Chronic thromboembolic pulmonary hypertension
Pulmonary tumor thrombotic microangiopathy

border or in the epigastrium. The increase in intensity of the holosystolic murmur of tricuspid regurgitation with inspiration (“Carvallo’s sign”) may be lost eventually as RV failure worsens. Cyanosis is a late finding in cor pulmonale and is secondary to a low cardiac output with systemic vasoconstriction and ventilation-perfusion mismatches in the lung.

DIAGNOSIS

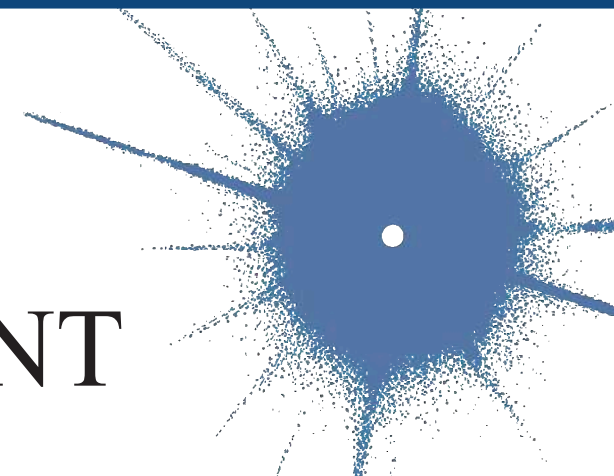
The most common cause of right HF is not pulmonary parenchymal or vascular disease but left HF. Therefore, it is important to evaluate the patient for LV systolic and diastolic dysfunction. The ECG in severe pulmonary hypertension shows P pulmonale, right axis deviation, and RV hypertrophy. Radiographic examination of the chest may show enlargement of the main central pulmonary arteries and hilar vessels. Spirometry and lung volumes can identify obstructive and/or restrictive defects indicative of parenchymal lung diseases; arterial blood gases can demonstrate hypoxemia and/or hypercapnia. Spiral computed tomography (CT) scans of the chest are useful in diagnosing acute thromboembolic disease; however, ventilation-perfusion lung scanning remains best suited for diagnosing chronic thromboembolic

disease (**Chap. 45**). A high-resolution CT scan of the chest can identify interstitial lung disease.

Two-dimensional echocardiography is useful for measuring RV thickness and chamber dimensions. Location of the RV behind the sternum and its crescent shape challenge assessment of RV function by echocardiography, especially when parenchymal lung disease is present. Calculated measures of RV function (e.g., tricuspid annular plane systolic excursion [TAPSE] or the Tei Index) supplement more subjective assessments of RV function. The interventricular septum may move paradoxically during systole in the presence of pulmonary hypertension. As noted, Doppler echocardiography can be used to assess pulmonary artery pressures. MRI is also useful for assessing RV structure and function, particularly in patients who are difficult to image with 2-D echocardiography because of severe lung disease. Right-heart catheterization is useful for confirming the diagnosis of pulmonary hypertension and for excluding elevated left-heart pressures (measured as the pulmonary capillary wedge pressure) as a cause for right HF. BNP and N-terminal BNP levels are elevated in patients with cor pulmonale secondary to RV myocardial stretch and may be dramatically elevated in acute pulmonary embolism.

CHAPTER 20

HEART FAILURE: MANAGEMENT



Mandeep R. Mehra

Distinctive phenotypes of presentation with diverse management targets exemplify the vast syndrome of heart failure. These range from chronic heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), acute decompensated heart failure (ADHF), and advanced heart failure. Early management evolved from symptom control to disease-modifying therapy in HFrEF with the advent of renin-angiotensin-aldosterone system (RAAS)-directed therapy, beta receptor antagonists, mineralocorticoid receptor antagonists, cardiac resynchronization therapy, and implantable cardio-defibrillators. However, similar advances have been elusive in the syndromes of HFpEF and ADHF, which have remained devoid of convincing therapeutic advances to alter their natural history. In advanced heart failure, a stage of disease typically encountered in HFrEF, the patient remains markedly symptomatic with demonstrated refractoriness or inability to tolerate full-dose neurohormonal antagonism, often requires escalating doses of diuretics, and exhibits persistent hyponatremia and renal insufficiency with frequent episodes of heart failure decompensation requiring recurrent hospitalizations. Such individuals are at the highest risk of sudden or progressive pump failure-related deaths (**Chap. 21**). In contrast, early-stage asymptomatic left ventricular dysfunction is amenable to preventive care, and its natural history is modifiable by neurohormonal antagonism (not further discussed).

HEART FAILURE WITH PRESERVED EJECTION FRACTION

GENERAL PRINCIPLES

Therapeutic targets in HFpEF include control of congestion, stabilization of heart rate and blood pressure, and efforts at improving exercise tolerance. Addressing surrogate targets, such as regression of ventricular hypertrophy in hypertensive heart disease, and use of

lusitropic agents, such as calcium channel blockers and beta receptor antagonists, have been disappointing. Experience has demonstrated that lowering blood pressure alleviates symptoms more effectively than targeted therapy with specific agents.

CLINICAL TRIALS IN HFpEF

The Candesartan in Heart Failure—Assessment of Mortality and Morbidity (CHARM) Preserved study showed a statistically significant reduction in hospitalizations but no difference in all-cause mortality in patients with HFpEF who were treated with the angiotensin receptor blocker (ARB), candesartan. Similarly, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial demonstrated no differences in meaningful endpoints in such patients treated with irbesartan. An earlier analysis of a subset of the Digitalis Investigation Group (DIG) trial found no role for digoxin in the treatment of HFpEF. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial of nebivolol, a vasodilating beta blocker, the subgroup of elderly patients with prior hospitalization and HFpEF did not appear to benefit in terms of all-cause or cardiovascular mortality. Much smaller mechanistic studies in the elderly with the angiotensin-converting enzyme inhibitor (ACEI) enalapril showed no effect on peak exercise oxygen consumption, 6-minute walk distance, aortic distensibility, left ventricular mass, or peripheral neurohormone expression.

NOVEL TARGETS

A small trial demonstrated that the phosphodiesterase-5 inhibitor sildenafil improved filling pressures and right ventricular function in a cohort of HFpEF patients with pulmonary venous hypertension. This finding led to the phase II trial, Phosphodiesterase-5 Inhibition

to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX), in HFpEF patients (left ventricular ejection fraction [LVEF] >50%) with New York Heart Association (NYHA) functional class II or III symptoms, who received sildenafil at 20 mg three times daily for 3 months, followed by 60 mg three times daily for another 3 months, compared with a placebo. There was no improvement in functional capacity, quality of life, or other clinical and surrogate parameters. Conceptually targeting myocardial fibrosis in HFpEF, the large-scale Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure (TOPCAT) trial has been completed. This trial demonstrated no improvement in the primary composite end-point, but did show a secondary signal of benefit on HF hospitalizations, counterbalanced, however, by an increase in adverse effects, particularly hyperkalemia. However, pessimism has been generated by the negative outcome of the Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study wherein spironolactone improved echocardiographic indices of diastolic dysfunction but failed to improve exercise capacity, symptoms, or quality-of-life

measures. A unique molecule that hybridizes an ARB with an endopeptidase inhibitor, LCZ696, increases the generation of myocardial cyclic guanosine 3',5'-monophosphate, enhances myocardial relaxation, and reduces ventricular hypertrophy. This dual blocker has been shown to reduce circulating natriuretic peptides and reduce left atrial size to a significantly greater extent than valsartan alone in patients with HFpEF.

CLINICAL PEARLS

Even as efforts to control hypertension in HFpEF are critical, evaluation for and correction of underlying ischemia may be beneficial. Appropriate identification and treatment of sleep-disordered breathing should be strongly considered. Excessive decrease in preload with vasodilators may lead to underfilling the ventricle and subsequent hypotension and syncope. Some investigators have suggested that the exercise intolerance in HFpEF is a manifestation of chronotropic insufficiency and that such aberrations could be corrected with use of rate responsive pacemakers, but this remains an inadequately investigated contention (Fig. 20-1).

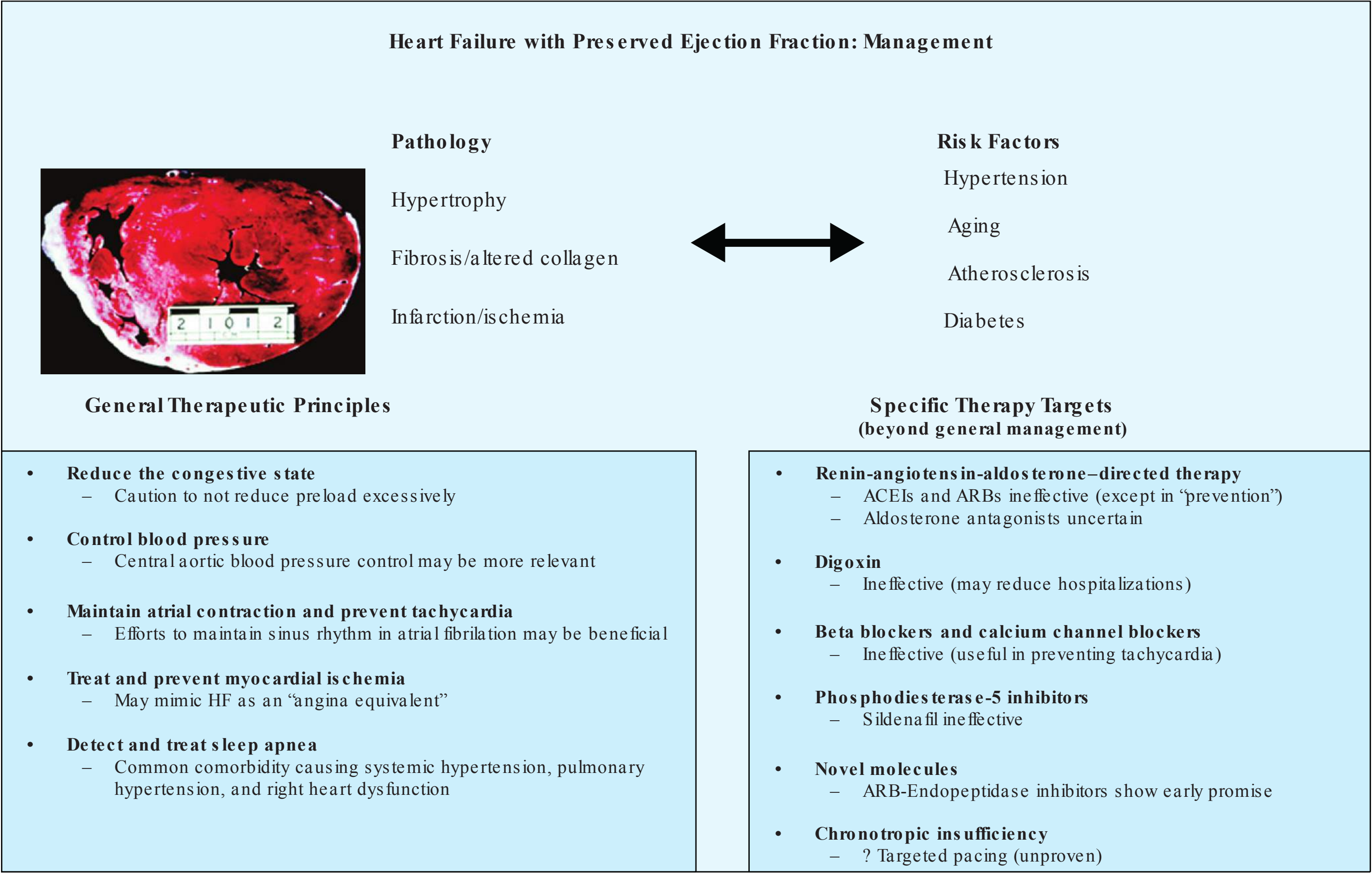


FIGURE 20-1
Pathophysiologic correlations, general therapeutic principles, and results of specific “directed” therapy in heart failure

(HF) with preserved ejection fraction. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

GENERAL PRINCIPLES

ADHF is a heterogeneous clinical syndrome most often resulting in need for hospitalization due to confluence of interrelated abnormalities of decreased cardiac performance, renal dysfunction, and alterations in vascular compliance. Admission with a diagnosis of ADHF is associated with excessive morbidity and mortality, with nearly half of these patients readmitted for management within 6 months, and a high short-term (5–8% in-hospital) and long-term mortality (20% at 1 year). Importantly, long-term aggregate outcomes remain poor, with a combined incidence of cardiovascular deaths, heart failure hospitalizations, myocardial infarction, strokes, or sudden death reaching 50% at 12 months after hospitalization. The management of these patients has remained difficult and principally revolves around volume control and decrease of vascular impedance while maintaining attention to end-organ perfusion (coronary and renal).

The first principle of management of these patients is to identify and tackle known precipitants of decompensation. Identification and management of medication nonadherence and use of prescribed medicines such as nonsteroidal anti-inflammatory drugs, cold and flu preparations with cardiac stimulants, and herbal preparations, including licorice, ginseng, and ma huang (an herbal form of ephedrine now banned in most places), are required. Active infection and overt or covert pulmonary thromboembolism should be sought, identified, and treated when clinical clues suggest such direction. When possible, arrhythmias should be corrected by controlling heart rate or restoring sinus rhythm in patients with poorly tolerated rapid atrial fibrillation and by correcting ongoing ischemia with coronary revascularization or by correcting offenders such as ongoing bleeding in demand-related ischemia. A parallel step in management involves stabilization of hemodynamics in those with instability. The routine use of a pulmonary artery catheter is not recommended and should be restricted to those who respond poorly to diuresis or experience hypotension or signs and symptoms suggestive of a low cardiac output where therapeutic targets are unclear. Analysis of in-hospital registries has identified several parameters associated with worse outcomes: a blood urea nitrogen level greater than 43 mg/dL (to convert to mmol/L, multiply by 0.357), systolic blood pressure less than 115 mmHg, a serum creatinine level greater than 2.75 mg/dL (to convert to μ mol/L, multiply by 88.4), and an elevated troponin I level. A useful clinical schema to identify treatment targets for the various phenotypic presentations and management goals in ADHF is depicted in [Fig. 20-2](#).

VOLUME MANAGEMENT

Intravenous diuretic agents

Intravenous diuretic agents rapidly and effectively relieve symptoms of congestion and are essential when oral drug absorption is impaired. When high doses of diuretic agents are required or when the effect is suboptimal, a continuous infusion may be needed to reduce toxicity and maintain stable serum drug levels. Randomized clinical trials of high-versus low-dose or bolus versus continuous infusion diuresis have not provided clear justification for the best diuretic strategy in ADHF, and as such, the use of diuretic regimens remains an art rather than science. Addition of a thiazide diuretic agent such as metolazone in combination provides a synergistic effect and is often required in patients receiving long-term therapy with loop diuretic agents. Change in weight is often used as a surrogate for adequate diuresis, but this objective measure of volume status may be surprisingly difficult to interpret, and weight loss during hospitalization does not necessarily correlate closely with outcomes. It is generally advisable to continue diuresis until euvolemia has been achieved. Physical examination findings, specifically the jugular venous pressure coupled with biomarker trends, are useful in timing discharge planning.

The cardiorenal syndrome

The cardiorenal syndrome is being recognized increasingly as a complication of ADHF. Multiple definitions have been proposed for the cardiorenal syndrome, but at its simplest, it can be thought to reflect the interplay between abnormalities of heart and kidney function, with deteriorating function of one organ while therapy is administered to preserve the other. Approximately 30% of patients hospitalized with ADHF exhibit abnormal renal function at baseline, and this is associated with longer hospitalizations and increased mortality. However, mechanistic studies have been largely unable to find correlation between deterioration in renal function, cardiac output, left-sided filling pressures, and reduced renal perfusion; most patients with cardiorenal syndrome demonstrate a preserved cardiac output. It is hypothesized that in patients with established heart failure, this syndrome represents a complex interplay of neurohormonal factors, potentially exacerbated by “backward failure” resulting from increased intra-abdominal pressure and impairment in return of renal venous blood flow. Continued use of diuretic therapy may be associated with a reduction in glomerular filtration rate and a worsening of the cardiorenal syndrome when right-sided filling pressures remain elevated. In patients in the late stages of disease characterized by profound low cardiac output state, inotropic therapy or mechanical circulatory support has been shown to

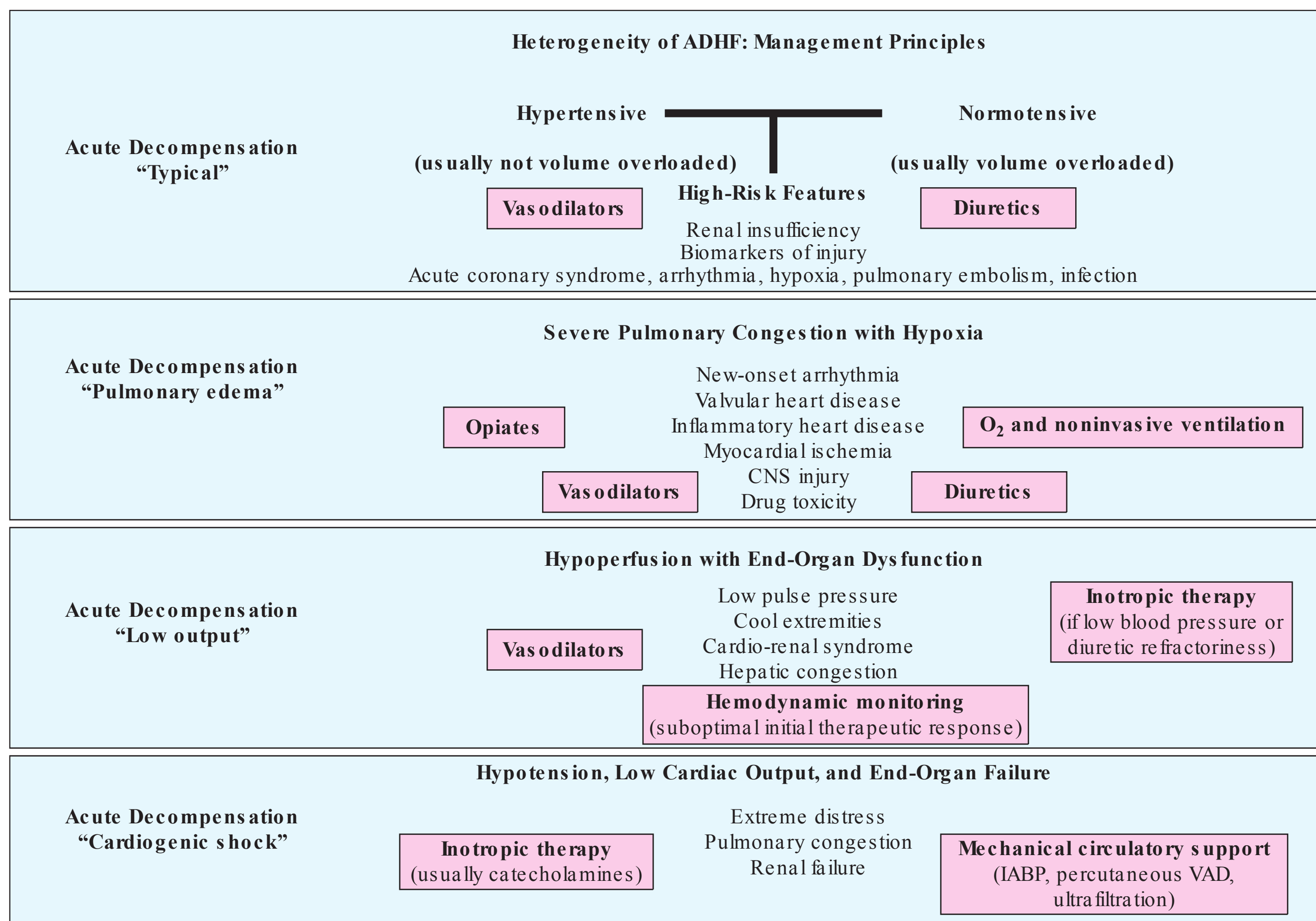


FIGURE 20-2

The distinctive phenotypes of acute decompensated heart failure (ADHF), their presentations, and suggested therapeutic routes. (Unique causes of ADHF, such as isolated right heart failure and pericardial disease, and rare causes, such

as aortic and coronary dissection or ruptured valve structures or sinuses of Valsalva, are not delineated and are covered elsewhere.) IABP, intraaortic balloon pump; VAD, ventricular assist device.

preserve or improve renal function in selected individuals in the short term until more definitive therapy such as assisted circulation or cardiac transplantation is implemented.

Ultrafiltration

Ultrafiltration (UF) is an invasive fluid removal technique that may supplement the need for diuretic therapy. Proposed benefits of UF include controlled rates of fluid removal, neutral effects on serum electrolytes, and decreased neurohormonal activity. This technique has also been referred to as aquapheresis in recognition of its electrolyte depletion-sparing effects. Current UF systems function with two large-bore, peripherally inserted venous lines. In a pivotal study evaluating UF versus conventional therapy, fluid removal was improved and subsequent heart failure hospitalizations and urgent clinic visits were reduced with UF; however, no improvement in renal function and no subjective

differences in dyspnea scores or adverse outcomes were noted. More recently, in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, 188 patients with ADHF and worsening renal failure were randomized to stepped pharmacologic care or UF. The primary endpoint was a change in serum creatinine and change in weight (reflecting fluid removal) at 96 hours. Although similar weight loss occurred in both groups (approximately 5.5 kg), there was worsening in creatinine in the UF group. Deaths and hospitalizations for heart failure were no different between groups, but there were more severe adverse events in the UF group, mainly due to kidney failure, bleeding complications, and intravenous catheter-related complications. This investigation argues against using UF as a primary strategy in patients with ADHF who are nonetheless responsive to diuretics. Whether UF is useful in states of diuretic unresponsiveness remains an open question, and this strategy continues to be employed judiciously in such situations.

VASCULAR THERAPY

Vasodilators including intravenous nitrates, nitroprusside, and nesiritide (a recombinant brain-type natriuretic peptide) have been advocated for upstream therapy in an effort to stabilize ADHF. The latter agent was introduced in a fixed dose for therapy after a comparison with intravenous nitrates suggested more rapid and greater reduction in pulmonary capillary wedge pressure. Enthusiasm for nesiritide waned due to concerns within the pivotal trials for development of renal insufficiency and an increase in mortality. To address these concerns, a large-scale morbidity and mortality trial, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) study was completed in 2011 and randomly enrolled 7141 patients with ADHF to nesiritide or placebo for 24 to 168 hours in addition to standard care. Nesiritide was not associated with an increase or a decrease in the rates of death and rehospitalization and had a clinically insignificant benefit on dyspnea. Renal function did not worsen, but increased rates of hypotension were noted. Although this trial established the safety for this drug, the routine use cannot be advocated due to lack of significant efficacy. Recombinant human relaxin-2, or serelaxin, is a peptide upregulated in pregnancy and examined in ADHF patients with a normal or elevated blood pressure. In the Relaxin in Acute Heart Failure (RELAX-AHF) trial, serelaxin or placebo was added to a regimen of standard therapy in 1161 patients hospitalized with ADHF, evidence of congestion, and systolic pressure >125 mmHg. Serelaxin improved dyspnea, reduced signs and symptoms of congestion, and was associated with less early worsening of HF. Exploratory endpoints of hard outcomes at 6 months suggested positive signals in favor of mortality reduction. This agent is being tested in a large, more confirmatory trial setting.

INOTROPIC THERAPY

Impairment of myocardial contractility often accompanies ADHF, and pharmacologic agents that increase intracellular concentration of cyclic adenosine monophosphate via direct or indirect pathways, such as sympathomimetic amines (dobutamine) and phosphodiesterase-3 inhibitors (milrinone), respectively, serve as positive inotropic agents. Their activity leads to an increase in cytoplasmic calcium. Inotropic therapy in those with a low-output state augments cardiac output, improves perfusion, and relieves congestion acutely. Although milrinone and dobutamine have similar hemodynamic profiles, milrinone is slower acting and is renally excreted and thus requires dose adjustments in the setting of kidney dysfunction. Since milrinone acts downstream from the β_1 -adrenergic receptor, it may provide an advantage in patients receiving beta blockers when admitted to

the hospital. Studies are in universal agreement that long-term inotropic therapy increases mortality. However, the short-term use of inotropic agents in ADHF is also associated with increased arrhythmia, hypotension, and no beneficial effects on hard outcomes. Inotropic agents are currently indicated as bridge therapy (to either left ventricular assist device support or to transplant) or as selectively applied palliation in end-stage heart failure.

Novel inotropic agents that leverage the concept of myofilament calcium sensitization rather than increasing intracellular calcium levels have been introduced. Levosimendan is a calcium sensitizer that provides inotropic activity, but also possesses phosphodiesterase-3 inhibition properties that are vasodilators in action. This makes the drug unsuitable in states of low output in the setting of hypotension. Two trials, the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) and Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), have tested this agent in ADHF. SURVIVE compared levosimendan with dobutamine, and despite an initial reduction in circulating B-type natriuretic peptide levels in the levosimendan group compared with patients in the dobutamine group, this drug did not reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. The second trial compared levosimendan against traditional noninotropic therapy and found a modest improvement in symptoms with worsened short-term mortality and ventricular arrhythmias. Another drug that functions as a selective myosin activator, omecamtiv mecarbil, prolongs the ejection period and increases fractional shortening. Distinctively, the force of contraction is not increased, and as such, this agent does not increase myocardial oxygen demand. In a 600-patient trial called ATOMIC-HF (A Trial of Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure), this agent showed improvement in dyspnea scores in the highest dose cohort, but not across all enrolled patients. How this agent performs in broader populations remains uncertain. Other inotropic agents that increase myocardial calcium sensitivity through mechanisms that reduce cTnI phosphorylation or inhibit protein kinase A are being developed. (Table 20-1 depicts typical inotropic, vasodilator, and diuretic drugs used in ADHF.)

NEUROHORMONAL ANTAGONISTS

Other trials testing unique agents have yielded disappointing results in the situation of ADHF. The Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial

TABLE 20-1

INTRAVENOUS THERAPY IN ACUTE DECOMPENSATED HEART FAILURE				
DRUG CLASS	GENERIC DRUG	USUAL DOSING	SPECIAL CAUTION	COMMENTS
Inotropic therapy	Dobutamine	2–20 µg/kg per min	Increased myocardial oxygen demand, arrhythmia	Use in hypotension, end-organ hypoperfusion, or shock states Short acting, an advantage; variable efficacy in presence of beta blockers (requires higher doses); clinical tolerance to prolonged infusions; concerns with hypersensitivity carditis (rare)
	Milrinone	0.375–0.75 µg/kg per min	Hypotension, arrhythmia	Decrease dose in renal insufficiency; avoid initial bolus; effectiveness retained in presence of beta blockers
	Levosimendan	0.1 µg/kg per min, range, 0.05–0.2 µg/kg per min	Hypotension, arrhythmia	Long acting; should not be used in presence of low blood pressure; similar effectiveness as dobutamine but effectiveness retained in presence of beta blockers
	Omecamtiv Mecarbil	N/A	*In trials	Increases contractility without increasing myocardial oxygen demand; in confirmatory trials
Vasodilators				Use in presence of pulmonary congestion for rapid relief of dyspnea, in presence of a preserved blood pressure
	Nitroglycerine	10–20 µg/min, increase up to 200 µg/min	Headache, flushing, tolerance	Most common vasodilator but often underdosed; effective in higher doses
	Nesiritide	Bolus 2 µg/kg and infusion at 0.01 µg/kg per min	Hypotension	Decrease in blood pressure may reduce renal perfusion pressure; bolus may be avoided since it increases hypotension predilection
	Nitroprusside	0.3 µg/kg per min titrated to 5 µg/kg per min	Thiocyanate toxicity in renal insufficiency (>72 hours)	Requires arterial line placement for titration for precise blood pressure management and prevention of hypotension
	Serelaxin	N/A (tested at 30 µg/kg per d)	Baseline blood pressure should be >125 mmHg	Not widely commercially available; undergoing confirmatory trials
Diuretics				First line of therapy in volume overload with congestion; may use bolus or continuous dosing; initial low dose (1× home dose) or high dose (2.5 × home dose) equally effective with higher risk of renal worsening with higher dose
	Furosemide	20–240 mg daily	Monitor for electrolyte loss	In severe congestion, use intravenously and consider continuous infusion (not trial supported)
	Torsemide	10–100 mg daily	Monitor for electrolyte loss	High bioavailability, can be given orally; anecdotally more effective in advanced heart failure states if furosemide less bioavailable (due to gut congestion)
	Bumetanide	0.5–5 mg daily	Monitor for electrolyte loss	Can be used orally; intermediate bioavailability
	Adjuvant diuretics for augmentation	n/a	Metolazone, chlorthalidone, spironolactone, acetazolamide	Acetazolamide is useful in presence of alkalosis; metolazone given in 2.5- to 10-mg doses; causes severe electrolyte imbalance; spironolactone is useful in presence of severe hypokalemia and normal renal function

230 of selective adenosine antagonism and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial of an oral selective vasopressin-2 antagonist in ADHF were both negative with respect to hard outcomes.

In patients who fail to respond adequately to medical therapy, mechanical assist devices may be required. This is covered in more detail in Chap. 21.

HEART FAILURE WITH REDUCED EJECTION FRACTION

The past 50 years have witnessed great strides in the management of HFrEF. The treatment of symptomatic heart failure that evolved from a renocentric (diuretics) and hemodynamic therapy model (digoxin, inotropic therapy) ushered in the era of disease-modifying therapy with neurohormonal antagonism. In this regard, ACEIs and beta blockers form the cornerstone of pharmacotherapy and lead to attenuation of decline and improvement in cardiac structure and function with consequent reduction in symptoms, improvement in quality of life, decreased burden of hospitalizations, and a decline in mortality from both pump failure and arrhythmic deaths (Fig. 20-3).

NEUROHORMONAL ANTAGONISM

Meta-analyses suggest a 23% reduction in mortality and a 35% reduction in the combination endpoint of mortality and hospitalizations for heart failure in patients treated with ACEIs. Patients treated with beta blockers provide a further 35% reduction in mortality on top of the benefit provided by ACEIs alone. Increased experience with both agents in a broad range of patients with HFrEF has demonstrated the safety of ACEIs in treating patients with mild renal insufficiency and the tolerability of beta blockers in patients with moderately controlled diabetes, asthma, and obstructive lung disease. The benefits of ACEIs and beta blockers extend to advanced symptoms of disease (NYHA class IIIb–IV). However, a substantial number of patients with advanced heart failure may not be able to achieve optimal doses of neurohormonal inhibitors and require cautious reduction in dose exposure to maintain clinical stability. Such individuals with lower exposure to ACEIs and beta blockers represent a high-risk cohort with poor prognosis.

Class effect and sequence of administration

ACEIs exert their beneficial effects in HFrEF as a class; however, the beneficial effects of beta blockers are

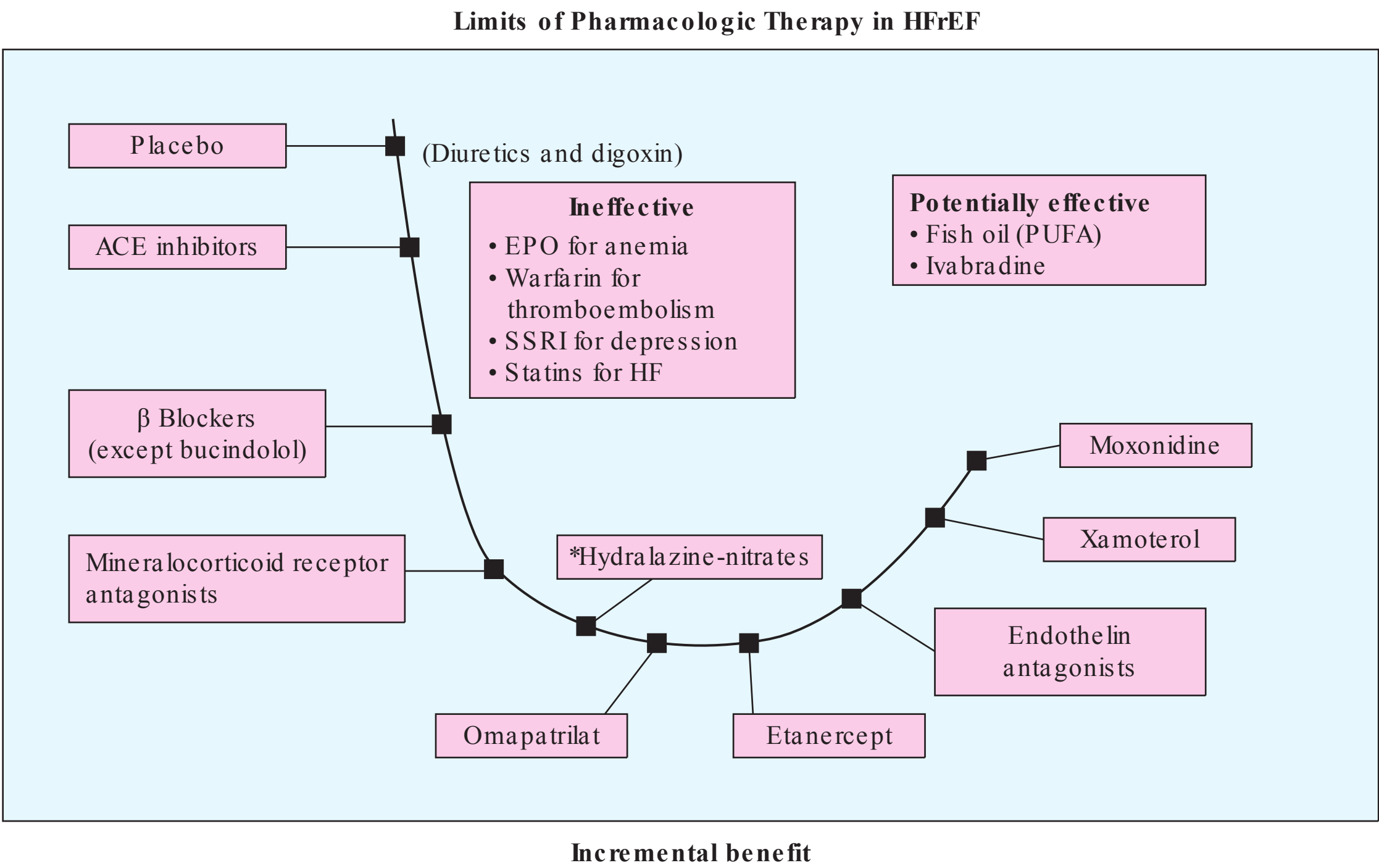


FIGURE 20-3

Progressive decline in mortality with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta blockers, mineralocorticoid receptor antagonists, and balanced vasodilators (*selected populations such as African Americans); further stack-on neurohormonal therapy is ineffective

or results in worse outcome; management of comorbidity is of unclear efficacy. EPO, erythropoietin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibitor.

thought to be limited to specific drugs. Beta blockers with intrinsic sympathomimetic activity (xamoterol) and other agents, including bucindolol, have not demonstrated a survival benefit. On the basis of investigations, beta blocker use in HFrEF should be restricted to carvedilol, bisoprolol, and metoprolol succinate—agents tested and proven to improve survival in clinical trials. Whether beta blockers or ACEIs should be started first was answered by the Cardiac Insufficiency Bisoprolol Study (CIBIS) III, in which outcomes did not vary when either agent was initiated first. Thus, it matters little which agent is initiated first; what does matter is that optimally titrated doses of both ACEIs and beta blockers be established in a timely manner.

Dose and Outcome

A trial has indicated that higher tolerated doses of ACEIs achieve greater reduction in hospitalizations without materially improving survival. Beta blockers demonstrate a dose-dependent improvement in cardiac function and reductions in mortality and hospitalizations. Clinical experience suggests that, in the absence of symptoms to suggest hypotension (fatigue and dizziness), pharmacotherapy may be up-titrated every 2 weeks in hemodynamically stable and euvolemic ambulatory patients as tolerated.

MINERALOCORTICOID ANTAGONISTS

Aldosterone antagonism is associated with a reduction in mortality in all stages of symptomatic NYHA class II to IV HFrEF. Elevated aldosterone levels in HFrEF promote sodium retention, electrolyte imbalance, and endothelial dysfunction and may directly contribute to myocardial fibrosis. The selective agent eplerenone (tested in NYHA class II and post-myocardial infarction heart failure) and the nonselective antagonist spironolactone (tested in NYHA class III and IV heart failure) reduce mortality and hospitalizations, with significant reductions in sudden cardiac death (SCD). Hyperkalemia and worsening renal function are concerns, especially in patients with underlying chronic kidney disease, and renal function and serum potassium levels must be closely monitored.

RAAS THERAPY AND NEUROHORMONAL “ESCAPE”

Neurohormonal “escape” has been witnessed in patients with HFrEF by the finding that circulating levels of angiotensin II return to pretreatment levels with long-term ACEI therapy. ARBs blunt this phenomenon by binding competitively to the AT₁ receptor. A large meta-analysis of 24 randomized trials showed the superiority of ARBs to placebo in patients with intolerable adverse

effects with ACEIs and their noninferiority in all-cause mortality or hospitalizations when compared with ACEIs. The Valsartan Heart Failure Trial (Val-HeFT) suggested that addition of valsartan in patients already receiving treatment with ACEIs and beta blockers was associated with a trend toward worse outcomes. Similarly, adding valsartan to captopril in patients with heart failure after myocardial infarction who were receiving background beta blocker therapy was associated with an increase in adverse events without any added benefit compared with monotherapy for either group. Thus, the initial clinical strategy should be to use a two-drug combination first (ACEI and beta blocker; if beta blocker intolerant, then ACEI and ARB; if ACEI intolerant, then ARB and beta blocker). In symptomatic patients (NYHA class II–IV), an aldosterone antagonist should be strongly considered, but four-drug therapy should be avoided.

A recent trial called the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) tested a direct renin inhibitor, aliskiren, in addition to other heart failure medications, within a week after discharge from a hospitalization for decompensated HFrEF. No significant difference in cardiovascular death or hospitalization at 6 or 12 months was noted. Aliskiren was associated with a reduction in circulating natriuretic peptides, but any disease-modifying effect was overcome by excessive adverse events including hyperkalemia, hypotension, and renal dysfunction.

ARTERIOVENOUS VASODILATION

The combination of hydralazine and nitrates has been demonstrated to improve survival in HFrEF. Hydralazine reduces systemic vascular resistance and induces arterial vasodilatation by affecting intracellular calcium kinetics; nitrates are transformed in smooth muscle cells into nitric oxide, which stimulates cyclic guanosine monophosphate production and consequent arterial-venous vasodilation. This combination improves survival, but not to the magnitude evidenced by ACEIs or ARBs. However, in individuals with HFrEF unable to tolerate renin-angiotensin-aldosterone-based therapy for reasons such as renal insufficiency or hyperkalemia, this combination is preferred as a disease-modifying approach. A trial conducted in self-identified African Americans, the African-American Heart Failure Trial (A-Heft), studied a fixed dose of isosorbide dinitrate with hydralazine in patients with advanced symptoms of HFrEF who were receiving standard background therapy. The study demonstrated benefit in survival and hospitalization recidivism in the treatment group. Adherence to this regimen is limited by the thrice-daily dosing schedule. **Table 20-2** lists the common neurohormonal and vasodilator regimens for HFrEF.

TABLE 20-2
PHARMACOLOGIC THERAPY AND TARGET DOSES IN HEART FAILURE WITH REDUCED EJECTION FRACTION

DRUG CLASS	GENERIC DRUG	MEAN DAILY DOSE IN CLINICAL TRIALS (mg)	INITIATION (mg)	TARGET DOSE (mg)
Angiotensin-Converting Enzyme Inhibitors				
	Lisinopril	4.5–33	2.5–5 qd	20–35 qd
	Enalapril	17	2.5 bid	10–20 bid
	Captopril	123	6.25 tid	50 tid
	Trandolapril	N/A	0.5–1 qd	4 qd
Angiotensin Receptor Blockers				
	Losartan	129	50 qd	150 qd
	Valsartan	254	40 bid	160 bid
	Candesartan	24	4–8 qd	32 qd
Aldosterone Antagonists				
	Eplerenone	42.6	25 qd	50 qd
	Spironolactone	26	12.5–25 qd	25–50 qd
Beta Blockers				
	Metoprolol succinate CR/XL	159	12.5–25 qd	200 qd
	Carvedilol	37	3.125 bid	25–50 bid
	Bisoprolol	8.6	1.25 qd	10 qd
Arteriovenous Vasodilators				
	Hydralazine isosorbide dinitrate	270/136	37.5/20 tid	75/40 tid
	Fixed-dose hydralazine/ isosorbide dinitrate	143/76	37.5/20 qid	75/40 qid

HEART RATE MODIFICATION

Ivabradine, an inhibitor of the I_f current in the sinoatrial node, slows the heart rate without a negative inotropic effect. The Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial (SHIFT) was conducted in patients with class II or III HFrEF, a heart rate >70 beats/min, and history of hospitalization for heart failure during the previous year. Ivabradine reduced hospitalizations and the combined endpoint of cardiovascular-related death and heart failure hospitalization. The study population was not necessarily representative of North American patients with HFrEF since, with a few exceptions, most did not receive internal cardioverter-defibrillation or cardiac resynchronization therapy and 40% did not receive a mineralocorticoid receptor antagonist. Although 90% received beta blockers, only a quarter were on full doses. Whether this agent, now available outside the United States, would have been effective in patients receiving robust, guideline-recommended therapy for heart failure remains enigmatic. In the 2012 European Society of Cardiology guidelines for the treatment of heart failure, ivabradine was suggested as second-line

therapy before digoxin is considered in patients who remain symptomatic after guideline-based ACEIs, beta blockers, and mineralocorticoid receptor antagonists and with residual heart rate >70 beats/min. Another group in whom potential benefit may be expected includes those unable to tolerate beta blockers.

DIGOXIN

Digitalis glycosides exert a mild inotropic effect, attenuate carotid sinus baroreceptor activity, and are sympathoinhibitory. These effects decrease serum norepinephrine levels, plasma renin levels, and possibly aldosterone levels. The DIG trial demonstrated a reduction in heart failure hospitalizations in the treatment group but no reduction in mortality or improvement in quality of life. Importantly, treatment with digoxin resulted in a higher mortality rate in women than men. Furthermore, the effects of digoxin in reducing hospitalizations were lower in women than in men. It should be noted that low doses of digoxin are sufficient to achieve any potentially beneficial outcomes, and higher

doses breach the therapeutic safety index. Although digoxin levels should be checked to minimize toxicity and although dose reductions are indicated for higher levels, no adjustment is made for low levels. Generally, digoxin is now relegated as therapy for patients who remain profoundly symptomatic despite optimal neurohormonal blockade and adequate volume control.

ORAL DIURETICS

Neurohormonal activation results in avid salt and water retention. Loop diuretic agents are often required because of their increased potency, and frequent dose adjustments may be necessary because of variable oral absorption and fluctuations in renal function. Importantly, clinical trial data confirming efficacy are limited, and no data suggest that these agents improve survival. Thus, diuretic agents should ideally be used in tailored dosing schedules to avoid excessive exposure. Indeed, diuretics are essential at the outset to achieve volume control before neurohormonal therapy is likely to be well tolerated or titrated.

CALCIUM CHANNEL ANTAGONISTS

Amlodipine and felodipine, second-generation calcium channel-blocking agents, safely and effectively reduce blood pressure in HFrEF but do not affect morbidity, mortality, or quality of life. The first-generation agents, including verapamil and diltiazem, may exert negative inotropic effects and destabilize previously asymptomatic patients. Their use should be discouraged.

NOVEL NEUROHORMONAL ANTAGONISM

Despite an abundance of animal and clinical data demonstrating deleterious effects of activated neurohormonal pathways beyond the RAAS and sympathetic nervous system, targeting such pathways with incremental blockade has been largely unsuccessful. As an example, the endothelin antagonist bosentan is associated with worsening heart failure in HFrEF despite demonstrating benefits in right-sided heart failure due to pulmonary arterial hypertension. Similarly, the centrally acting sympatholytic agent moxonidine worsens outcomes in left heart failure. The combined drug omapatrilat hybridizes an ACEI with a neutral endopeptidase inhibitor, and this agent was tested in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVER-TURE) trial. This drug did not favorably influence the primary outcome measure of the combined risk of death or hospitalization for heart failure requiring intravenous treatment. The risk of angioedema was notably higher with omapatrilat than ACEIs alone. LCZ696 and ARB with an endopeptidase inhibitor have shown benefit in a large trial versus ARB alone.

INFLAMMATION

Targeting inflammatory cytokines such as tumor necrosis factor α (TNF- α) by using anticytokine agents such as infliximab and etanercept has been unsuccessful and associated with worsening heart failure. Nonspecific immunomodulation has been tested in the large Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy (ACCLAIM-HF) trial of 2426 HFrEF patients with NYHA functional class II to IV symptoms. Ex vivo exposure of a blood sample to controlled oxidative stress initiates apoptosis of leukocytes soon after intramuscular gluteal injection of the treated sample. The physiologic response to apoptotic cells results in a reduction in inflammatory cytokine production and upregulation of anti-inflammatory cytokines. This promising hypothesis was not proven, although certain subgroups (those with no history of previous myocardial infarction and those with mild heart failure) showed signals in favor of immunomodulation. Use of intravenous immunoglobulin therapy in nonischemic etiology of heart failure has not been shown to result in beneficial outcomes.

STATINS

Potent lipid-altering and pleiotropic effects of statins reduce major cardiovascular events and improve survival in non-heart failure populations. Once heart failure is well established, this therapy may not be as beneficial and theoretically could even be detrimental by depleting ubiquinone in the electron transport chain. Two trials, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiac (GISSI-HF), have tested low-dose rosuvastatin in patients with HFrEF and demonstrated no improvement in aggregate clinical outcomes. If statins are required to treat progressive coronary artery disease in the background setting of heart failure, then they should be employed. However, no rationale appears to exist for routine statin therapy in nonischemic heart failure.

ANTICOAGULATION AND ANTIPLATELET THERAPY

HFrEF is accompanied by a hypercoagulable state and therefore a high risk of thromboembolic events, including stroke, pulmonary embolism, and peripheral arterial embolism. Although long-term oral anticoagulation is established in certain groups, including patients with atrial fibrillation, the data are insufficient to support the use of warfarin in patients in normal sinus rhythm without a history of thromboembolic events or echocardiographic evidence of left ventricular thrombus. In the large Warfarin versus Aspirin in Reduced Cardiac

Ejection Fraction (WARCEF) trial, 2305 patients with HFrEF were randomly allocated to either full-dose aspirin or international normalized ratio–controlled warfarin with follow-up for 6 years. Among patients with reduced LVEF who were in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. Aspirin blunts ACEI-mediated prostaglandin synthesis, but the clinical importance of this finding remains unclear. Current guidelines support the use of aspirin in patients with ischemic cardiomyopathy.

FISH OIL

Treatment with long-chain omega-3 polyunsaturated fatty acids (ω -3 PUFAs) has been shown to be associated with modestly improved clinical outcomes in patients with HFrEF. This observation from the GISSI-HF trial was extended to measurements of ω -3 PUFAs in plasma phospholipids at baseline and after 3 months. Three-month treatment with ω -3 PUFAs enriched circulating eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Low EPA levels are inversely related to total mortality in patients with HFrEF.

MICRONUTRIENTS

A growing body of evidence suggests an association between heart failure and micronutrient status. Reversible heart failure has been described as a consequence of severe thiamine and selenium deficiency. Thiamine deficiency has received attention in heart failure due to the fact that malnutrition and diuretics are prime risk factors for thiamine loss. Small exploratory randomized studies have suggested a benefit of supplementation of thiamine in HFrEF with evidence of improved cardiac function. This finding is restricted to chronic heart failure states and does not appear to be beneficial in the ADHF phenotype. Due to the preliminary nature of the evidence, no recommendations for routine supplementation or testing for thiamine deficiency can be made.

ENHANCED EXTERNAL COUNTERPULSATION (EECP)

Peripheral lower extremity therapy using graded external pneumatic compression at high pressure is administered in 1-hour sessions for 35 treatments (7 weeks) and has been proposed to reduce angina symptoms and extend time to exercise-induced ischemia in patients with coronary artery disease. The Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) study assessed the benefits of enhanced external counterpulsation in the treatment

of patients with mild-to-moderate heart failure. This randomized trial improved exercise tolerance, quality of life, and NYHA functional classification but without an accompanying increase in peak oxygen consumption. A placebo effect due to the nature of the intervention simply cannot be excluded.

EXERCISE

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study investigated short-term (3-month) and long-term (12-month) effects of a supervised exercise training program in patients with moderate HFrEF. Exercise was safe, improved patients' sense of well-being, and correlated with a trend toward mortality reduction. Maximal changes in 6-minute walk distance were evident at 3 months with significant improvements in cardiopulmonary exercise time and peak oxygen consumption persisting at 12 months. Therefore, exercise training is recommended as an adjunctive treatment in patients with heart failure.

MANAGEMENT OF SELECTED COMORBIDITY

Sleep-disordered breathing is common in HF and particularly in HFrEF. A range of presentations exemplified by obstructive sleep apnea, central sleep apnea, and its extreme form of Cheyne-Stokes breathing are noted. Frequent periods of hypoxia and repeated micro- and macro-arousals trigger adrenergic surges, which can worsen hypertension and impair systolic and diastolic function. A high index of suspicion is required, especially in patients with difficult-to-control hypertension or with predominant symptoms of fatigue despite reverse remodeling in response to optimal medical therapy. Worsening of right heart function with improvement of left ventricular function noted on medical therapy should immediately trigger a search for underlying sleep-disordered breathing or pulmonary complications such as occult embolism or pulmonary hypertension. Treatment with nocturnal positive airway pressure improves oxygenation, LVEF, and 6-minute walk distance. However, no conclusive data exist to support this therapy as a disease-modifying approach with reduction in mortality.

Anemia is common in heart failure patients, reduces functional status and quality of life, and is associated with increased proclivity for hospital admissions and mortality. Anemia in heart failure is more common in the elderly, in those with advanced stages of HFrEF, in the presence of renal insufficiency, and in women and African Americans. The mechanisms include iron deficiency, dysregulation of iron metabolism, and occult gastrointestinal bleeding. Intravenous iron using either

iron sucrose or carboxymaltose (Ferric Carboxymaltose Assessment in Patients with Iron Deficiency and Chronic Heart Failure [FAIR-HF] trial) has been shown to correct anemia and improve functional capacity. Erythropoiesis-regulating agents such as erythropoietin analogues have been studied with disappointing results. The Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial evaluated 2278 mild-to-moderate anemia patients with HFrEF and demonstrated that treatment with darbepoetin alfa did not improve clinical outcomes in patients with systolic heart failure.

Depression is common in HFrEF, with a reported prevalence of one in five patients, and is associated with a poor quality of life, limited functional status, and increased risk of morbidity and mortality in this population. Antidepressants may improve depression, promote vascular health, and decrease systemic inflammation in HFrEF. However, the largest randomized study of depression in HFrEF, the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) trial, showed that sertraline was safe, but did not provide greater reduction in depression or improve cardiovascular status among patients with heart failure and depression compared with nurse-driven multidisciplinary management.

Atrial arrhythmias, especially atrial fibrillation, are common and serve as a harbinger of worse prognosis in patients with heart failure. When rate control is inadequate or symptoms persist, pursuing a rhythm control strategy is reasonable. Rhythm control may be achieved via pharmacotherapy or by percutaneous or surgical techniques, and referral to practitioners or centers experienced in these modalities is recommended. Antiarrhythmic drug therapy should be restricted to amiodarone and dofetilide, both of which have been shown to be safe and effective but do not alter the natural history of the underlying disease. The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) studied the effects of the novel antiarrhythmic agent dronedarone and found an increased mortality due to worsening heart failure. Catheter ablation and pulmonary vein isolation appear to be safe and effective in this high-risk cohort and compare favorably with the more established practice of atrioventricular node ablation and biventricular pacing.

CARDIAC RESYNCHRONIZATION THERAPY

Nonsynchronous contraction between the walls of the left ventricle (intraventricular) or between the ventricular chambers (interventricular) impairs systolic function, decreases mechanical efficiency of

contraction, and adversely affects ventricular filling. Mechanical dyssynchrony results in an increase in wall stress and worsens functional mitral regurgitation. The single most important association of extent of dyssynchrony is a widened QRS interval on the surface electrocardiogram, particularly in the presence of a left bundle branch block pattern. With placement of a pacing lead via the coronary sinus to the lateral wall of the ventricle, cardiac resynchronization therapy (CRT) enables a more synchronous ventricular contraction by aligning the timing of activation of the opposing walls. Early studies showed improved exercise capacity, reduction in symptoms, and evidence of reverse remodeling. The Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial was the first study to demonstrate a reduction in all-cause mortality with CRT placement in patients with HFrEF on optimal therapy with continued moderate-to-severe residual symptoms of NYHA class III or IV heart failure. More recent clinical trials have demonstrated disease-modifying properties of CRT in even minimally symptomatic patients with HFrEF, including the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), both of which sought to use CRT in combination with an implantable defibrillator. Most benefit in mildly symptomatic HFrEF patients accrues from applying this therapy in those with a QRS width of >149 ms and a left bundle branch block pattern. Attempts to further optimize risk stratification and expand indications for CRT using modalities other than electrocardiography have proven disappointing. In particular, echocardiographically derived measures of dyssynchrony vary tremendously, and narrow QRS dyssynchrony has not proven to be a good target for treatment. Uncertainty surrounds the benefits of CRT in those with ADHF, a predominant right bundle branch block pattern, atrial fibrillation, and evidence of scar in the lateral wall, which is the precise location where the CRT lead is positioned.

SUDDEN CARDIAC DEATH PREVENTION IN HEART FAILURE

SCD due to ventricular arrhythmias is the mode of death in approximately half of patients with heart failure and is particularly proportionally prevalent in HFrEF patients with early stages of the disease. Patients who survive an episode of SCD are considered to be at very high risk and qualify for placement of an implantable cardioverter-defibrillator (ICD). Although primary prevention is challenging, the degree of residual left ventricular dysfunction despite optimal medical

236 therapy ($\leq 35\%$) to allow for adequate remodeling and the underlying etiology (post–myocardial infarction or ischemic cardiomyopathy) are the two single most important risk markers for stratification of need and benefit. Currently, patients with NYHA class II or III symptoms of heart failure and an LVEF $< 35\%$, irrespective of etiology of heart failure, are appropriate candidates for ICD prophylactic therapy. In patients with a myocardial infarction and optimal medical therapy with residual LVEF $\leq 30\%$ (even when asymptomatic), placement of an ICD is appropriate. In patients with a terminal illness and a predicted life span of less than 6 months or in those with NYHA class IV symptoms who are refractory to medications and who are not candidates for transplant, the risks of multiple ICD shocks must be carefully weighed against the survival benefits. If a patient meets the QRS criteria for CRT, combined CRT with ICD is often employed (Table 20-3).

TABLE 20-3
PRINCIPLES OF ICD IMPLANTATION FOR PRIMARY PREVENTION OF SUDDEN DEATH

PRINCIPLE	COMMENT
Arrhythmia–sudden death mismatch	Sudden death in heart failure patients is generally due to progressive LVD, not a focal arrhythmia substrate (except in patients with post-MI HF)
Diminishing returns with advanced disease	Intervention at early stages of HF most successful since sudden death diminishes as cause of death with advanced HF
Timing of benefits	LVEF should be evaluated on optimal medical therapy or after revascularization before ICD therapy is employed; no benefit to ICD implant within 40 days of an MI (unless for secondary prevention)
Estimation of benefits and prognosis	Patients and clinicians often overestimate benefits of ICDs; an ICD discharge is not equivalent to an episode of sudden death (some ventricular arrhythmias terminate spontaneously); appropriate ICD discharges are associated with a worse near-term prognosis

Abbreviations: HF, heart failure; ICD, implantable cardioverter-defibrillator; LVD, left ventricular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

SURGICAL THERAPY IN HEART FAILURE

Coronary artery bypass grafting (CABG) is considered in patients with ischemic cardiomyopathy with multivessel coronary artery disease. The recognition that hibernating myocardium, defined as myocardial tissue with abnormal function but maintained cellular function, could recover after revascularization led to the notion that revascularization with CABG would be useful in those with living myocardium. Revascularization is most robustly supported in individuals with ongoing angina and left ventricular failure. Revascularizing those with left ventricular failure in the absence of angina remains controversial. The Surgical Treatment for Ischemic Heart Failure (STICH) trial enrolled 1212 patients with an ejection fraction of 35% or less and coronary artery disease amenable to CABG and randomly assigned them to medical therapy alone or medical therapy plus CABG. There was no significant difference between groups with respect to the primary endpoint of death from any cause. Patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes. An ancillary study of this trial also determined that the detection of hibernation pre-revascularization did not materially influence the efficacy of this approach, nor did it help to define a population unlikely to benefit if hibernation was not detected.

Surgical ventricular restoration (SVR), a technique characterized by infarct exclusion to remodel the left ventricle by reshaping it surgically in patients with ischemic cardiomyopathy and dominant anterior left ventricular dysfunction, has been proposed. However, in a 1000-patient trial in patients with HFrEF who underwent CABG alone or CABG plus SVR, the addition of SVR to CABG had no disease-modifying effect. Cardiac symptoms and exercise tolerance improved from baseline to a similar degree in both study groups. SVR resulted in lower left ventricular volumes at 4 months after operation. However, left ventricular aneurysm surgery is still advocated in those with refractory heart failure, ventricular arrhythmias, or thromboembolism arising from an akinetic aneurysmal segment of the ventricle. Other remodeling procedures, such as use of an external mesh-like net attached around the heart to limit further enlargement, have not been shown to provide hard clinical benefits, although favorable cardiac remodeling was noted.

Mitral regurgitation (MR) occurs with varying degrees in patients with HFrEF and dilated ventricles. Annular dilatation and leaflet noncoaptation in the setting of anatomically normal papillary muscles, chordal structures, and valve leaflets characterize functional MR. In patients who are not candidates for surgical coronary revascularization, mitral valve repair remains controversial. Ischemic MR (or infarct-related MR) is

typically associated with leaflet tethering and displacement related to abnormal left ventricular wall motion and geometry. No evidence to support the use of surgical or percutaneous valve correction for functional MR exists as disease-modifying therapy even though MR can be corrected.

CELLULAR AND GENE-BASED THERAPY

The cardiomyocyte is no longer considered a terminally differentiated cell and possesses regenerative capacity. Such renewal is accelerated under conditions of stress and injury, such as an ischemic event or heart failure. Investigations that use either bone marrow-derived precursor cells or autologous cardiac-derived cells have gained traction. A number of small- and moderate-scale trials of such therapy have focused on post-myocardial infarction patients and have used autologous bone marrow-derived progenitor or stem cells. These trials have had variable results, with most demonstrating modest improvements in parameters of cardiac structure and remodeling. More promising, however, are cardiac-derived stem cells. Two preliminary pilot trials delivering cells via an intracoronary approach have been reported. In one, autologous c-kit-positive cells isolated from the atria obtained from patients undergoing CABG were cultured and reinfused. In another, cardiosphere-derived cells grown from endomyocardial biopsy specimens were used. These small trials demonstrated improvements in left ventricular function but require far more work to usher in a clinical therapeutic success. The appropriate route of administration, the quantity of cells to achieve a minimal therapeutic threshold, the constitution of these cells (single source or mixed), the mechanism by which benefit accrues, and short- and long-term safety remain to be elucidated.

Targeting molecular aberrations using gene transfer therapy, mostly with an adenoviral vector, is emerging in HFrEF. Several methods of gene delivery have been developed, including direct intramyocardial injection, coronary artery or venous infusion, and injection into the pericardial space. Cellular targets under consideration include β_2 -adrenergic receptors and calcium cycling proteins such as inhibitors of phospholamban. SERCA2a is deficient in patients with HFrEF and is primarily responsible for reincorporating calcium into the sarcoplasmic reticulum during diastole. A phase II randomized, double-blind, placebo-controlled trial called CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure) was completed. This study used coronary arterial infusion of adeno-associated virus type 1 carrying the gene for SERCA2a and demonstrated that natriuretic peptides were decreased, reverse remodeling

was noted, and symptomatic improvements were forthcoming. Stromal-derived factor 1 enhances myocardial repair and facilitates “homing” of stem cells to the site of tissue injury. Strategies using intramyocardial injections to deploy this gene at sites of injury are being studied.

More advanced therapies for late-stage heart failure such as left ventricular assist devices and cardiac transplantation are covered in detail in Chap. 21.

DISEASE MANAGEMENT AND SUPPORTIVE CARE

Despite stellar outcomes with medical therapy, admission rates following heart failure hospitalization remain high, with nearly half of all patients readmitted to hospital within 6 months of discharge. Recurrent heart failure and related cardiovascular conditions account for only half of readmissions in patients with heart failure, whereas other comorbidity-related conditions account for the rest. The key to achieving enhanced outcomes must begin with the attention to transitional care at the index hospitalization with facilitated discharge through comprehensive discharge planning, patient and caregiver education, appropriate use of visiting nurses, and planned follow-up. Early postdischarge follow-up, whether by telephone or clinic-based, may be critical to ensuring stability because most heart failure-related readmissions tend to occur within the first 2 weeks after discharge. Although routinely advocated, intensive surveillance of weight and vital signs with use of telemonitoring has not decreased hospitalizations. Intrathoracic impedance measurements have been advocated for the identification of early rise in filling pressure and worsened hemodynamics so that preemptive management may be employed. However, this has not been successful and may worsen outcomes in the short term. Implantable pressure monitoring systems do tend to provide signals for early decompensation, and in patients with moderately advanced symptoms, such systems have been shown to provide information that can allow implementation of therapy to avoid hospitalizations by as much as 39% (in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients [CHAMPION] trial). Once heart failure becomes advanced, regularly scheduled review of the disease course and options with the patient and family is recommended including discussions surrounding end-of-life preferences when patients are comfortable in an outpatient setting. As the disease state advances further, integrating care with social workers, pharmacists, and community-based nursing may be critical in improving patient satisfaction with the therapy, enhancing quality of life, and avoiding heart failure hospitalizations.

238 Equally important is attention to seasonal influenza vaccinations and periodic pneumococcal vaccines that may obviate non–heart failure hospitalizations in these ill patients. When nearing end of life, facilitating a shift in priorities to outpatient and hospice palliation is key, as are discussions around advanced therapeutics and continued use of ICD prophylaxis, which may worsen quality of life and prolong death.

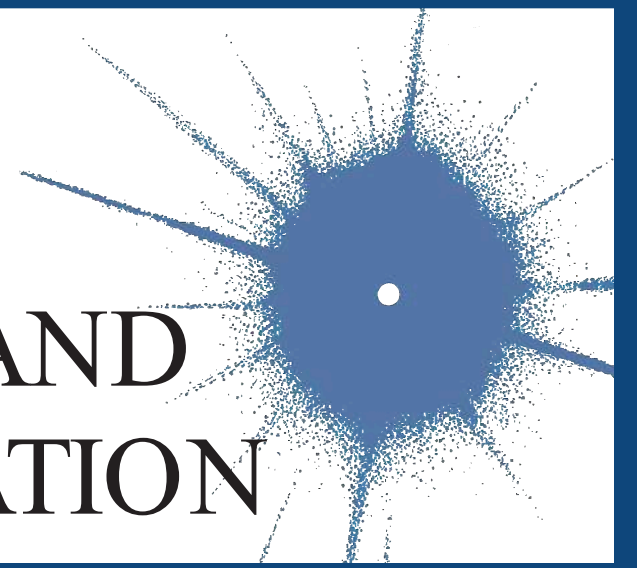
GLOBAL CONSIDERATIONS

Substantial differences exist in the practice of heart failure therapeutics and outcomes by geographic location. International guidelines produced by the American College of Cardiology/American Heart Association, European Society of Cardiology, and National Institute for Health and Clinical Excellence (United Kingdom) differ in their approach to evaluation of evidence and prioritization of therapy. The penetrance of CRT and ICD is higher in the United States than in Europe. Conversely, therapy unavailable

in the United States, such as ivabradine and levosimendan, is designated as useful in Europe. Although ACEIs appear to be similarly effective across populations, variation in the benefits of beta blockers based on world region remains an area of controversy. In oral pharmacologic therapy trials of HFrEF, patients from southwest Europe have a lower incidence of ischemic cardiomyopathy and those in North America tend to have more diabetes and prior coronary revascularization. There is also regional variation in medication use even after accounting for indication. In trials of ADHF, patients in Eastern Europe tend to be younger, with higher ejection fractions and lower natriuretic peptide levels. Patients from South America tend to have the lowest rates of comorbidities, revascularization, and device use. In contrast, patients from North America have the highest comorbidity burden with high revascularization and device use rates. Given geographic differences in baseline characteristics and clinical outcomes, the generalizability of therapeutic outcomes in patients in the United States and Western Europe may require verification.

CHAPTER 21

CARDIAC TRANSPLANTATION AND PROLONGED ASSISTED CIRCULATION



Sharon A. Hunt ■ Hari R. Mallidi

Advanced or end-stage heart failure is an increasingly frequent sequela of many types of heart disease, as progressively more effective palliation for the earlier stages of heart disease and prevention of sudden death associated with heart disease become more widely recognized and employed (**Chap. 19**). When patients with end-stage or refractory heart failure are identified, the physician is faced with the decision of advising compassionate end-of-life care or choosing to recommend extraordinary life-extending measures. For the occasional patient who is relatively young and without serious comorbidities, the latter may represent a reasonable option. Current therapeutic options are limited to cardiac transplantation (with the option of mechanical cardiac assistance as a “bridge” to transplantation) or permanent mechanical assistance of the circulation. In the future, it is possible that genetic modulation of ventricular function or cell-based cardiac repair will be options for such patients. Currently, both of the latter approaches are considered to be experimental.

CARDIAC TRANSPLANTATION



Surgical techniques for orthotopic transplantation of the heart were devised in the 1960s and taken into the clinical arena in 1967. The procedures did not gain widespread clinical acceptance until the introduction of “modern” and more effective immunosuppression in the early 1980s. By the 1990s, the demand for transplantable hearts met, and then exceeded, the available donor supply and leveled off at about 4000 heart transplantations annually worldwide, according to data from the Registry of the International Society for Heart and Lung Transplantation (ISHLT). Subsequently, heart transplantation activity in the United States has remained stable at ~2200 per year, but

worldwide activity reported to this registry has decreased somewhat. The apparent decline in numbers may be a result of the fact that reporting is legally mandated in the United States but not elsewhere, and several countries have started their own databases.

SURGICAL TECHNIQUE

Donor and recipient hearts are excised in virtually identical operations with incisions made across the atria and atrial septum at the mid-atrial level (with the posterior walls of the atria left in place) and across the great vessels just above the semilunar valves. The donor heart is generally “harvested” by a separate surgical team, transported from the donor hospital in a bag of iced saline solution, and reanastomosed into the waiting recipient in the orthotopic or normal anatomic position. The only change in surgical technique since this method was first described has been a movement in recent years to move the right atrial anastomosis back to the level of the superior and inferior venae cavae to better preserve right atrial geometry and prevent atrial arrhythmias. Both methods of implantation leave the recipient with a surgically denervated heart that does not respond to any direct sympathetic or parasympathetic stimuli but does respond to circulating catecholamines. The physiologic responses of the denervated heart to the demands of exercise are atypical but quite adequate for continuation of normal physical activity.

DONOR ALLOCATION SYSTEM

In the United States, the allocation of donor organs is accomplished under the supervision of the United Network for Organ Sharing, a private organization under contract to the federal government. The United States is divided geographically into eleven regions for donor

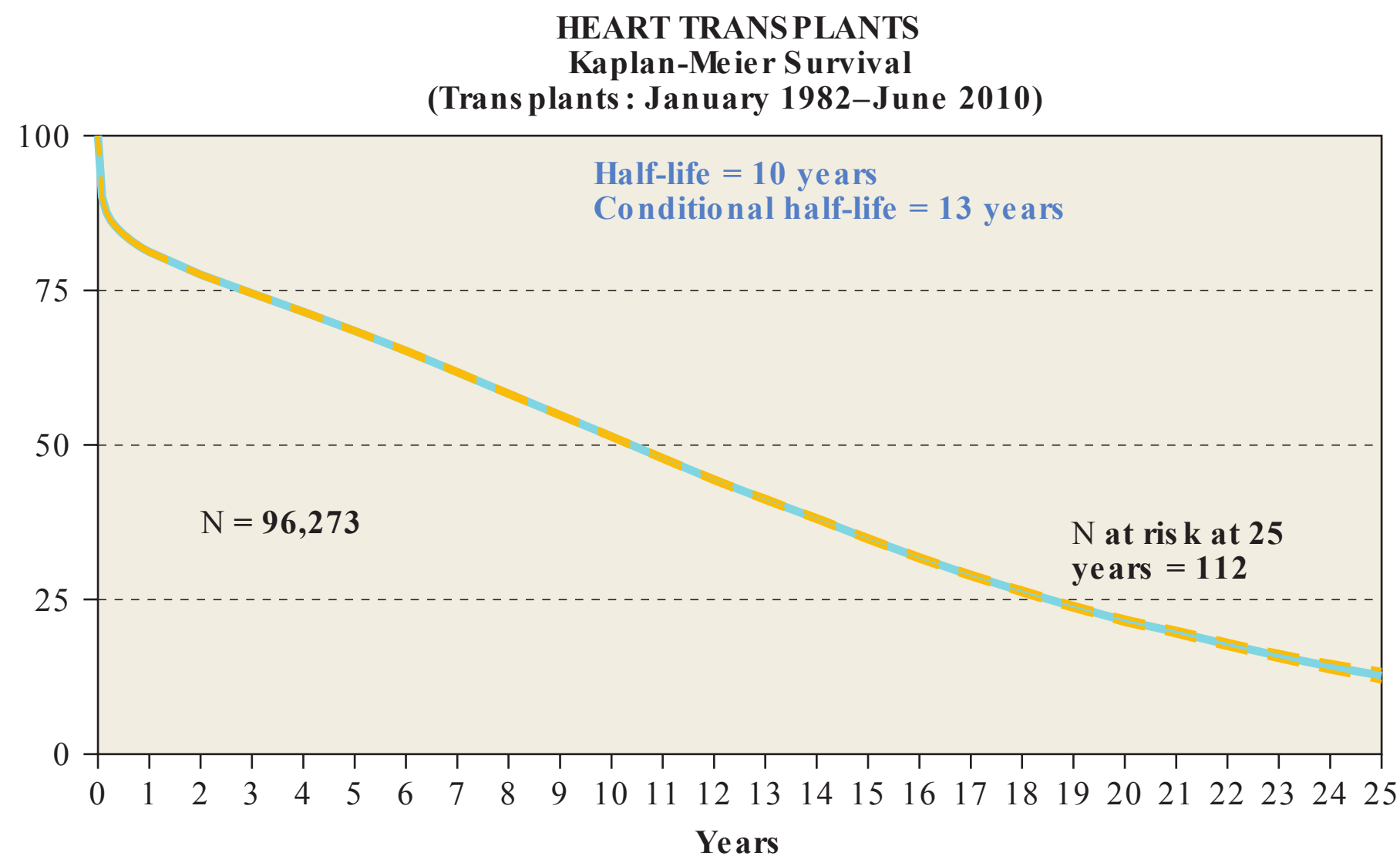


FIGURE 21-1

Global survival rates after heart transplantation since 1982. Rates were calculated by the Kaplan-Meier method, which incorporates information from all transplant recipients for whom any follow-up has been provided. Because many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact figures because the time of death is not known for all patients. Therefore, 95% confidence limits are provided. (From J Stehlik et al: *J Heart Lung Transplant* 31:1052, 2012.)

heart allocation. Allocation of donor hearts within a region is decided according to a system of priority that takes into account (1) the severity of illness, (2) the geographic distance from the donor, and (3) the patient's time on the waiting list. A physiologic limit of ~3 h of "ischemic" (out-of-body) time for hearts precludes a national sharing of hearts. This allocation system design is reissued annually and is responsive to input from a variety of constituencies, including both donor families and transplantation professionals.

At the current time, the highest priority according to severity of illness is assigned to patients requiring hospitalization at the transplantation center for IV inotropic support, with a pulmonary artery catheter in place for hemodynamic monitoring, or to patients requiring mechanical circulatory support—i.e., use of an intra-aortic balloon pump or a right or left ventricular assist device (RVAD, LVAD), extracorporeal membrane oxygenation, or mechanical ventilation. The second highest priority is given to patients requiring ongoing inotropic support, but without a pulmonary artery catheter in place. All other patients are assigned a priority according to time accrued on the waiting list, and matching generally is based only on compatibility in terms of ABO blood group and gross body size.

While HLA matching of donor and recipient would be ideal, the relatively small numbers of patients as well as the time constraints involved make such matching impractical. However, some patients who

are "presensitized" and have preexisting antibodies to human leukocyte antigens (HLAs) undergo prospective cross-matching with the donor; these patients are commonly multiparous women or patients who have received multiple transfusions.

INDICATIONS/CONTRAINDICATIONS

Heart failure is an increasingly common cause of death, particularly in the elderly. Most patients who reach what has recently been categorized as stage D, or refractory end-stage heart failure, are appropriately treated with compassionate end-of-life care. A subset of such patients who are younger and without significant comorbidities can be considered as candidates for heart transplantation. Exact criteria vary in different centers but generally take into consideration the patient's physiologic age and the existence of comorbidities such as peripheral or cerebrovascular disease, obesity, diabetes, cancer, or chronic infection.

RESULTS



A registry organized by the ISHLT has tracked worldwide and U.S. survival rates after heart transplantation since 1982. The most recent update reveals survival rates of 83% and 76% 1 and 3 years after transplantation, respectively, or a posttransplantation "half-life" of 10.00 years (**Fig. 21-1**). The

quality of life of survivors is generally excellent, with well over 90% of patients in the registry returning to normal and unrestricted function after transplantation.

IMMUNOSUPPRESSION

Medical regimens employed to suppress the normal immune response to a solid organ allograft vary from center to center and are in a constant state of evolution, as more effective agents with improved side-effect profiles and less toxicity are introduced. All currently used regimens are nonspecific, providing general hyporeactivity to foreign antigens rather than donor-specific hyporeactivity and also causing the attendant, and unwanted, susceptibility to infections and malignancy. Most cardiac transplantation programs currently use a three-drug regimen that includes a calcineurin inhibitor (cyclosporine or tacrolimus), an inhibitor of T cell proliferation or differentiation (azathioprine, mycophenolate mofetil, or sirolimus), and at least a short initial course of glucocorticoids. Many programs also include an initial “induction” course of polyclonal or monoclonal antibodies to T cells in the perioperative period to decrease the frequency or severity of early posttransplantation rejection. Most recently introduced have been monoclonal antibodies (daclizumab and basiliximab) that block the interleukin 2 receptor and may prevent allograft rejection without additional global immunosuppression.

Cardiac allograft rejection is usually diagnosed by endomyocardial biopsy conducted either on a surveillance basis or in response to clinical deterioration. Biopsy surveillance is performed on a regular basis in most programs for the first year postoperatively (or the first 5 years in many programs). Therapy consists of augmentation of immunosuppression, the intensity and duration of which are dictated by the severity of rejection.

LATE POSTTRANSPLANTATION MANAGEMENT ISSUES

Increasing numbers of heart transplant recipients are surviving for years following transplantation and constitute a population of patients with a number of long-term management issues.

Allograft Coronary Artery Disease

Despite usually having young donor hearts, cardiac allograft recipients are prone to develop coronary artery disease (CAD). This CAD is generally a diffuse, concentric, and longitudinal process that is quite different from “ordinary” atherosclerotic CAD, which is more focal and often eccentric. The underlying etiology most

likely is primarily immunologic injury of the vascular endothelium, but a variety of risk factors influence the existence and progression of CAD, including nonimmunologic factors such as dyslipidemia, diabetes mellitus, and cytomegalovirus (CMV) infection. It is hoped that newer and improved immunosuppressive modalities will reduce the incidence and impact of these devastating complications, which currently account for the majority of late posttransplantation deaths. Thus far, the immunosuppressive agents mycophenolate mofetil and the mammalian target of the rapamycin (mTOR) inhibitors sirolimus and everolimus have been shown to be associated with short-term lower incidence and extent of coronary intimal thickening; in anecdotal reports, institution of sirolimus was associated with some reversal of CAD. The use of statins also is associated with a reduced incidence of this vasculopathy, and these drugs are now used almost universally in transplant recipients unless contraindicated. Palliation of CAD with percutaneous interventions is probably safe and effective in the short term, although the disease often advances relentlessly. Because of the denervated status of the organ, patients rarely experience angina pectoris, even in advanced stages of disease.

Retransplantation is the only definitive form of therapy for advanced allograft CAD. However, the scarcity of donor hearts makes the decision to pursue retransplantation in an individual patient difficult and ethically complex.

Malignancy

An increased incidence of malignancy is a well-recognized sequela of any program of chronic immunosuppression, and organ transplantation is no exception. Lymphoproliferative disorders are among the most frequent posttransplantation complications and, in most cases, seem to be driven by Epstein-Barr virus. Effective therapy includes reduction of immunosuppression (a clear “double-edged sword” in the setting of a life-sustaining organ), administration of antiviral agents, and traditional chemo- and radiotherapy. Most recently, specific antilymphocyte (CD20) therapy has shown great promise. Cutaneous malignancies (both basal cell and squamous cell carcinomas) also occur with increased frequency among transplant recipients and can follow aggressive courses. The role of decreasing immunosuppression in the treatment of these cancers is far less clear.

Infections

The use of currently available nonspecific immunosuppressive modalities to prevent allograft rejection naturally results in increased susceptibility to infectious complications in transplant recipients. Although

the incidence has decreased since the introduction of cyclosporine, infections with unusual and opportunistic organisms are still the major cause of death during the first postoperative year and remain a threat to the chronically immunosuppressed patient throughout life. Effective therapy depends on careful surveillance for early signs and symptoms of opportunistic infection, an extremely aggressive approach to obtaining a specific diagnosis, and expertise in recognizing the more common clinical presentations of infections caused by CMV, *Aspergillus*, and other opportunistic agents.

PROLONGED ASSISTED CIRCULATION

The modern era of mechanical circulatory support can be traced back to 1953, when cardiopulmonary bypass was first used in a clinical setting and ushered in the possibility of brief periods of circulatory support to permit open-heart surgery. Subsequently, a variety of extracorporeal pumps to provide circulatory support for brief periods have been developed. The use of a mechanical device to support the circulation for more than a few hours initially progressed slowly, with the implantation of a total artificial heart in 1969 in Texas by Cooley. This patient survived for 60 h until a donor organ became available, at which point he underwent transplantation. Unfortunately, the patient died of pulmonary complications after transplantation. The entire field of mechanical replacement of the heart then took a decade-long hiatus until the 1980s, when total artificial hearts were reintroduced with much publicity; however, they failed to produce the hoped-for treatment of end-stage heart disease. Starting in the 1970s, in parallel with the development of the total artificial heart, intense research had addressed the development of ventricular assist devices, which provide mechanical assistance for (rather than replacing) the failing ventricle.

Although conceived of initially as alternatives to biologic replacement of the heart, LVADs were introduced—and are still employed primarily—as temporary “bridges” to heart transplantation in candidates in whom medical therapy begins to fail before a donor heart becomes available. Several devices are approved by the U.S. Food and Drug Administration (FDA) and are in widespread use (see later). Those that are implantable within the body are compatible with hospital discharge and offer the patient a chance for life at home during a wait for a donor heart. However successful such “bridging” is for the individual patient, it does nothing to alleviate the scarcity of donor hearts; the ultimate goal in the field remains that of providing a reasonable alternative to biologic replacement of the heart—one that is widely and easily available and cost-effective.

CURRENT INDICATIONS AND APPLICATIONS OF VENTRICULAR ASSIST DEVICES

Currently, there are two major indications for ventricular assistance. First, patients at risk of imminent death from cardiogenic shock are eligible for mechanical support. These patients are generally managed with temporary cardiac assist devices. Second, if patients have a left ventricular ejection fraction $<25\%$ or a peak $\text{VO}_2 <14$ mL/kg per min or are dependent on inotropic therapy or support with intra-aortic balloon counterpulsation, they may be eligible for mechanical support. If they are eligible for heart transplantation, the mechanical circulatory assistance is termed the “bridge to transplantation.” By contrast, if the patient has a contraindication to heart transplantation, the use of the device is deemed to constitute “destination” left ventricular assistance therapy.

BASIC CONCEPTS

Pulsatile vs. nonpulsatile devices

Pulsatile devices are ventricular assist devices whose mechanism of action mandates the alternating filling and emptying of a volume chamber within the device that mimics the mechanism of action of the natural heart. Nonpulsatile devices have a mechanism of action that results in continuous blood flow through the device, eliminating the need for pulsatility. The pulsatile devices are larger, bulkier, and associated with greater energy requirements and higher rates of complications than the nonpulsatile devices. However, pulsatile devices provide greater degrees of support and may even be capable of replacing the function of the heart entirely in the form of a total artificial heart. Because of the bulkiness of these devices, many patients are too small to be supported with intracorporeal pulsatile pumps. However, paracorporeal versions are available. These devices are versatile and can be used for right, left, or biventricular assistance/replacement.

Continuous-flow (nonpulsatile) devices are further categorized on the basis of impeller design and mechanism. The older designs have tended to be axial-flow pumps, which operate on the Archimedes screw principle. These devices have an impeller that is in line with the direction of blood flow, and the inlet direction of blood is the same as the outlet direction. Continuous-flow devices have been dependent on the presence of blood-washed bearings within the pump housing and may be associated with an increased risk of blood and platelet activation. The newer devices are centrifugal in design; the blood flow takes a 90° turn between the inlet

section of the pump and the outlet section. Another major difference in the newer devices is the absence of blood-washed bearings (with most devices having magnetically levitated impellers). This design allows the construction of smaller pumps with less blood-element activation than the axial-flow designs.

Available Devices

In the United States, there are currently four FDA-approved devices that are used as bridges to transplantation in adults. Of these four devices, one is also approved for use as destination therapy or as long-term mechanical support of the heart. A number of other devices are approved only for short-term support in post-cardiac surgery shock or in cardiogenic shock secondary to acute myocardial infarction or fulminant myocarditis; these will not be considered here. So far, no long-term device is totally implantable, and, because of the need for transcutaneous connections, all share a common problem with infectious complications. Likewise, all share some tendency to thromboembolic complications and are subject to the possibility of mechanical failure common to any machine.

The total artificial heart (TAH) (Syncardia, Tucson, AZ) is a pneumatic, biventricular, orthotopically implanted ventricular assist device with an externalized driveline connecting it to its console. The TAH is currently the only FDA-approved device for use in patients who have severe biventricular failure.

The Thoratec LVAD (Thoratec Corp., Pleasanton, CA) is an extracorporeal pump that takes blood from a large cannula placed in the left ventricular apex and propels it forward through an outflow cannula inserted into the ascending aorta. The extracorporeal nature of this pump allows its use in small adults for whom intracorporeal pumps would be too large. This device provides not only left but also right ventricular assistance and can be utilized for biventricular support within the same patient (BiVentricular Assist Device).

The HeartMate II LVAD (Thoratec) similarly uses a drainage cannula in the left ventricular apex to drain blood into a small chamber, where the blood is driven by an electrically powered motor that spins a rotor, accelerating blood outflow into the ascending aorta (Fig. 21-2). This device is currently the only FDA-approved axial-flow pump that can be used both as a bridge to transplantation and as destination therapy.

The HeartWare Ventricular Assist System with the HVAD pump (HeartWare Inc., Framingham, MA) is the first third-generation device to be granted FDA approval for use in patients as a bridge to transplantation. The device is a centrifugal pump that is housed completely within the patient's pericardial cavity and provides adequate support for many patients.

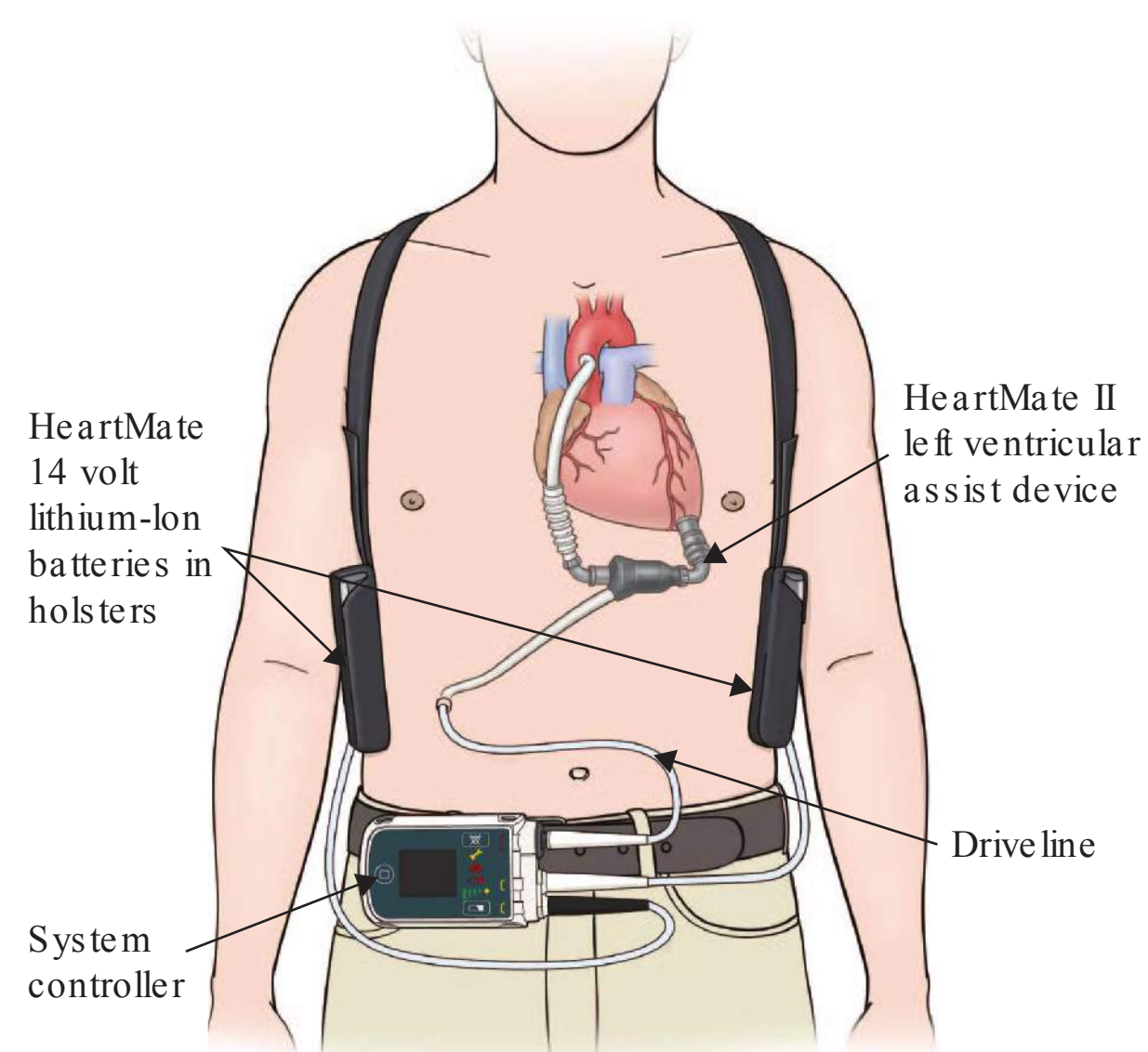


FIGURE 21-2

Diagram of HeartMate II left ventricular assist device (LVAD). (Reprinted with permission from Thoratec Corp., Pleasanton, CA.)

RESULTS

The use of these devices in the United States is limited mainly to patients with post-cardiac surgery shock and to those who are bridged to transplantation. The results of bridging to transplantation with the available devices are quite good, with nearly 75% of younger patients receiving a transplant by 1 year and having excellent posttransplantation survival rates.

Publication of the REMATCH (Randomized Evaluation of Mechanical Assistance in the Treatment of Heart Failure) trial in 2001 documented a somewhat improved survival rate in patients who had end-stage heart disease, were not candidates for transplantation, and were randomized to a pulsatile LVAD (albeit with a high rate of complications, especially neurologic issues) as opposed to continued medical therapy. This result led to renewed interest in use of the devices for nonbiologic permanent replacement of heart function as well. Subsequently, this device was supplanted by the HeartMate II axial-flow device, which has dramatically improved the survival of patients with severe end-stage heart disease in whom medical therapy has failed. The patients who had this device implanted had a 2-year survival rate of 58%, whereas the survival rate for patients in the medically treated arm of the original REMATCH trial was only 8%. More recent experience has shown that the mean survival period of patients with a continuous-flow LVAD for destination therapy is approaching 5 years.

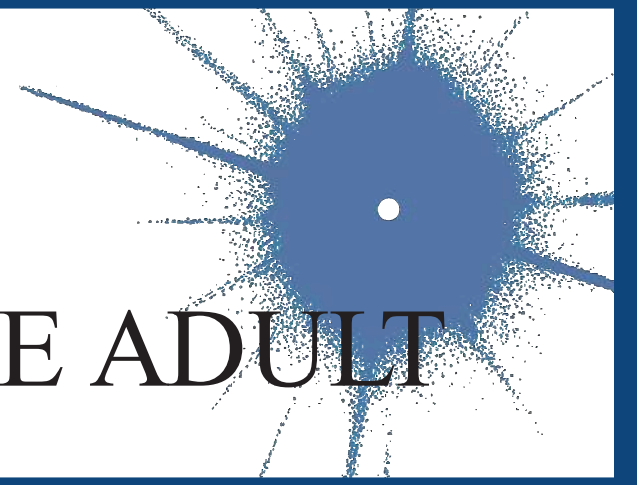
Several studies have evaluated the benefit of LVAD therapy as a bridge to transplantation. The most recent

data come from a series of 140 patients who underwent implantation of a HeartWare HVAD. Of these patients, 94% achieved the principal outcome (defined as survival to transplantation, recovery of heart function, or ongoing device support) at 180 days. With increased experience and improved outcomes using LVADs as a bridge to transplantation, the ability to maintain end-organ function and limit the progression of pulmonary hypertension—or even to decrease pulmonary vascular

resistance—makes mechanical unloading a more attractive option than continued inotropic support. The early bridge-to-transplantation experience demonstrated reduced posttransplantation survival compared with medical management; however, more recent experience has shown equivalent outcomes following transplantation. This result is likely secondary to a trend toward earlier device implantation—i.e., prior to the onset of irreversible end-organ damage.

CHAPTER 22

CONGENITAL HEART DISEASE IN THE ADULT



Jamil A. Aboulhosn ■ John S. Child

Over a hundred years ago, Sir William Osler, in his classic textbook *The Principles and Practice of Medicine* (New York, Appleton & Co, 1892, pp 659–663), devoted only five pages to “Congenital Affections of the Heart,” with the first sentence declaring that “[t]hese [disorders] have only limited clinical interest, as in a large proportion of cases the anomaly is not compatible with life, and in others nothing can be done to remedy the defect or even to relieve symptoms.” Fortunately, in the intervening century, considerable progress has been made in understanding the basis for these disorders and their effective treatment.

The most common birth defects are cardiovascular in origin. These malformations are due to complex multifactorial genetic and environmental causes. Recognized chromosomal aberrations and mutations of single genes account for <10% of all cardiac malformations. Congenital heart disease (CHD) complicates ~1% of all live births in the general population—about 40,000 births/year—but occurs more frequently in the offspring (about 4–10%, depending on maternal CHD type) of women with CHD. Owing to the remarkable surgical advances over the last 60 years, >90% of afflicted neonates and children now reach adulthood; women with CHD may now frequently successfully bear children after competent repairs. As such, the population with CHD is steadily increasing. Women with CHD are at increased risk for peri- and postpartum complications, but maternal CHD is generally not considered an absolute contraindication to pregnancy unless the mother has certain high-risk features (e.g., cyanosis, pulmonary hypertension, decompensated heart failure, arrhythmias, aortic aneurysm, among others). Consultation with an adult CHD expert is warranted for all females with CHD who desire to become pregnant.

Nearly one and a half million adults with operated or unoperated CHD live in the United States today; there are now more adults than children with CHD in the United States. Because true surgical cures are rare, and

all repairs—be they palliative or corrective—may leave residua, sequelae, or complications, most require some degree of lifetime expert surveillance. The anatomic and physiologic changes in the heart and circulation due to any specific CHD lesion are not static but, rather, progress from prenatal life to adulthood. Malformations that are benign or escape detection in childhood may become clinically significant in the adult. Unfortunately, the growing number of adults with CHD has not been paralleled by an adequate increase in the number of specialists and specialty centers that are trained and equipped to manage this challenging population. Ongoing efforts to increase awareness, resources, and advocacy are essential for the necessary growth of this specialty.

CARDIAC DEVELOPMENT

(See also Chap. 1) CHD is generally the result of aberrant embryonic development of a normal structure or failure of such a structure to progress beyond an early stage of embryonic or fetal development. This brief section serves to introduce the reader to normal development so that defects may be better understood; by necessity, it is not exhaustive. Cardiogenesis is a finely tuned process with transcriptional control of a complex group of regulatory proteins that activate or inhibit their gene targets in a location- and time-dependent manner. At about 3 weeks of embryonic development, two cardiac cords form and become canalized; at that point, the primordial cardiac tube develops from two sources (cardiac crescent or the first heart field, pharyngeal mesoderm or the second heart field); by 21 days, these fuse into a single cardiac tube beginning at the cranial end. The cardiac tube then elongates and develops discrete constrictions with the following segments from caudal to cranial location: sinus venosus receives the umbilical, vitelline, and common cardinal veins:

246 atrium, ventricle, bulbus cordis, truncus arteriosus, aortic sac, and the aortic arches. The cardiac tube is fixed at the sinus venosus and arterial ends.

Subsequently, in the next few weeks, differential growth of cells causes the tube to elongate and loop as an “S” with the bulboventricular portion moving rightward and the atrium and sinus venosus moving posterior to the ventricle. The primitive atrium and ventricle communicate via the atrioventricular canal from which the endocardial cushion develops into two parts (ventrally and dorsally). The cushions fuse and divide the atrioventricular canal into two atrioventricular inlets and also migrate to help form the ventricular septum. The primitive atrium is divided first by a septum primum membrane, which grows down from the superior wall to the cushions; as this fusion occurs, the mid-portion resorbs in the center forming the ostium secundum. Rightward of the septum primum, a second septum secundum membrane grows down from the ventral-cranial wall toward—but not reaching—the cushions, and covering most, but not all, of the ostium secundum, resulting in a flap of the foramen ovale. The primitive ventricle is partitioned by a finely tuned set of events. The interventricular septum grows up toward the cushions, and the cushions form an upper inlet septum; between the two portions is a hole called the interventricular foramen. The left and right ventricles begin to develop side by side, and the atria and their respective inlet valves align over their ventricles. Finally, these two parts of the septum fuse with the bulboventricular ridges, which, once having septated the truncus arteriosus, extend into the ventricle. The bulbocordis divides into a subaortic portion as the muscular conus resorbs, whereas the subpulmonary section has elongation of its muscular conus. Spiral division of the common truncus arteriosus rotates and aligns the pulmonary artery and aortic portions over their respective outflow tracts, the aortic valve moving posterior over the left ventricle (LV) outflow tract and the pulmonary valve moving anterior over the right ventricle (RV) outflow tract, with a wraparound relationship of the two great arteries.

Early on, the venous systems are bilateral and symmetric and enter two horns of the sinus venosus. Ultimately, except for the coronary sinus, most of the left-sided portions and the left sinus–venosus horn regress, and the systemic venous system empties into the right horn via the inferior and superior vena cavae. The pulmonary venous system, initially connecting to the systemic venous system, develops as buds from the developing lungs, which fuse together in the pulmonary venous confluence, at which point the connection to the systemic system regresses. Simultaneously, a projection from the back wall of the left atrium (the common pulmonary vein) grows posteriorly to merge with the confluence, which then becomes a part of the posterior left atrial wall.

The truncus arteriosus and aortic sac initially develop six paired symmetric arches, which curve posteriorly and become the paired dorsal aortae. The detailed description of the selective regression of some of the arches is not presented in this chapter. In brief summary, this process results in the development of arch 3 as the internal carotid arteries, left arch 4 as the aortic arch and right subclavian artery, and part of arch 6 as the patent ductus arteriosus. The two dorsal thoracic aortae fuse in the abdomen with persistence of the left dorsal aorta.

SPECIFIC CARDIAC DEFECTS

Tables 22-1, 22-2, and 22-3 list CHD malformations as simple, intermediate, or complex. Simple defects generally are single lesions with a shunt or a valvular malformation. Intermediate defects may have two or more simple defects. Complex defects generally have components of an intermediate defect plus more complex

TABLE 22-1

SIMPLE ADULT CONGENITAL HEART DISEASE	
Native disease	Uncomplicated congenital aortic valve disease
	Mild congenital mitral valve disease (e.g., except parachute valve, cleft leaflet)
	Uncomplicated small atrial septal defect
	Uncomplicated small ventricular septal defect
	Mild pulmonic stenosis
Repaired conditions	Previously ligated or occluded ductus arteriosus
	Repaired secundum or sinus venosus atrial septal defect without residua
	Repaired ventricular septal defect without residua

TABLE 22-2

INTERMEDIATE COMPLEXITY CONGENITAL HEART DISEASE	
	Ostium primum or sinus venosus atrial septal defect
	Anomalous pulmonary venous drainage, partial or total
	Atrioventricular canal defects (partial or complete)
	Ventricular septal defect, complicated (e.g., absent or abnormal valves or with associated obstructive lesions, aortic regurgitation)
	Coarctation of the aorta
	Pulmonic valve stenosis (moderate to severe)
	Infundibular right ventricular outflow obstruction of significance
	Pulmonary valve regurgitation (moderate to severe)
	Patent ductus arteriosus (nonclosed)—moderate to large
	Sinus of Valsalva fistula/aneurysm
	Subvalvular or supra-valvular aortic stenosis

TABLE 22-3

COMPLEX ADULT CONGENITAL HEART DISEASE

Cyanotic congenital heart diseases (all forms)
 Eisenmenger's syndrome
 Ebstein's anomaly
 Tetralogy of Fallot or pulmonary atresia (all forms)
 Transposition of the great arteries
 Single ventricle; tricuspid or mitral atresia
 Double-outlet ventricle
 Truncus arteriosus
 Fontan or Rastelli procedures

cardiac and vascular anatomy, often with cyanosis, and frequently with transposition complexes. The goal of these tables is to suggest when cardiology consultation or advanced CHD specialty care is needed. Patients with complex CHD (which includes most “named” surgeries that usually involve complex CHD) should virtually always be managed in conjunction with an experienced specialty adult CHD center. Patients with intermediate lesions should have an initial consultation and subsequent occasional intermittent follow-up with an adult CHD specialist. Patients with simple lesions often may be managed by a well-informed internist or general cardiologist, although consultation with a specifically trained adult congenital cardiologist is occasionally advisable.

ATRIAL SEPTAL DEFECT

Atrial septal defect (ASD) is a common cardiac anomaly that may be first encountered in the adult and occurs more frequently in females. Sinus venosus ASD occurs high in the atrial septum near the entry of the superior vena cava into the right atrium and is associated frequently with anomalous pulmonary venous connection from the right lung to the superior vena cava or right atrium (Fig. 22-1). Ostium primum ASDs lie adjacent to the atrioventricular valves, either of which may be deformed and regurgitant. Ostium primum ASDs are common in Down's syndrome, often as part of complex atrioventricular septal defects with a common atrioventricular valve and a posterior defect of the basal portion of the interventricular septum. The most common ostium secundum ASD involves the fossa ovalis and is midseptal in location; this should not be confused with a patent foramen ovale. Anatomic obliteration of the foramen ovale ordinarily follows its functional closure soon after birth, but residual “probe patency” is a common normal variant; ASD denotes a true deficiency of the atrial septum and implies functional and anatomic patency. The magnitude of the left-to-right shunt depends on the ASD size, ventricular diastolic properties, and the relative impedance in the pulmonary and systemic circulations. The left-to-right

shunt causes diastolic overloading of the RV and increased pulmonary blood flow. Patients with ASD are usually asymptomatic in early life, although there may be some physical underdevelopment and an increased tendency for respiratory infections; cardiorespiratory symptoms occur in many older patients. Beyond the fourth decade, a significant number of patients develop atrial arrhythmias, pulmonary arterial hypertension, and right heart failure. Patients exposed to the chronic environmental hypoxemia of high altitude tend to develop pulmonary hypertension at younger ages. In older patients, left-to-right shunting across the ASD increases as progressive systemic hypertension and/or coronary artery disease (CAD) result in reduced compliance of the LV.

Physical examination

Examination usually reveals a prominent RV impulse and palpable pulmonary artery pulsation. The first heart sound is normal or split, with accentuation of the tricuspid valve closure sound. Increased flow across the pulmonic valve is responsible for a midsystolic pulmonary outflow murmur. The second heart sound is widely split and is fixed in relation to respiration. A mid-diastolic rumbling murmur, loudest at the fourth intercostal space and along the left sternal border, reflects increased flow across the tricuspid valve. In ostium primum ASD, an apical holosystolic murmur indicates

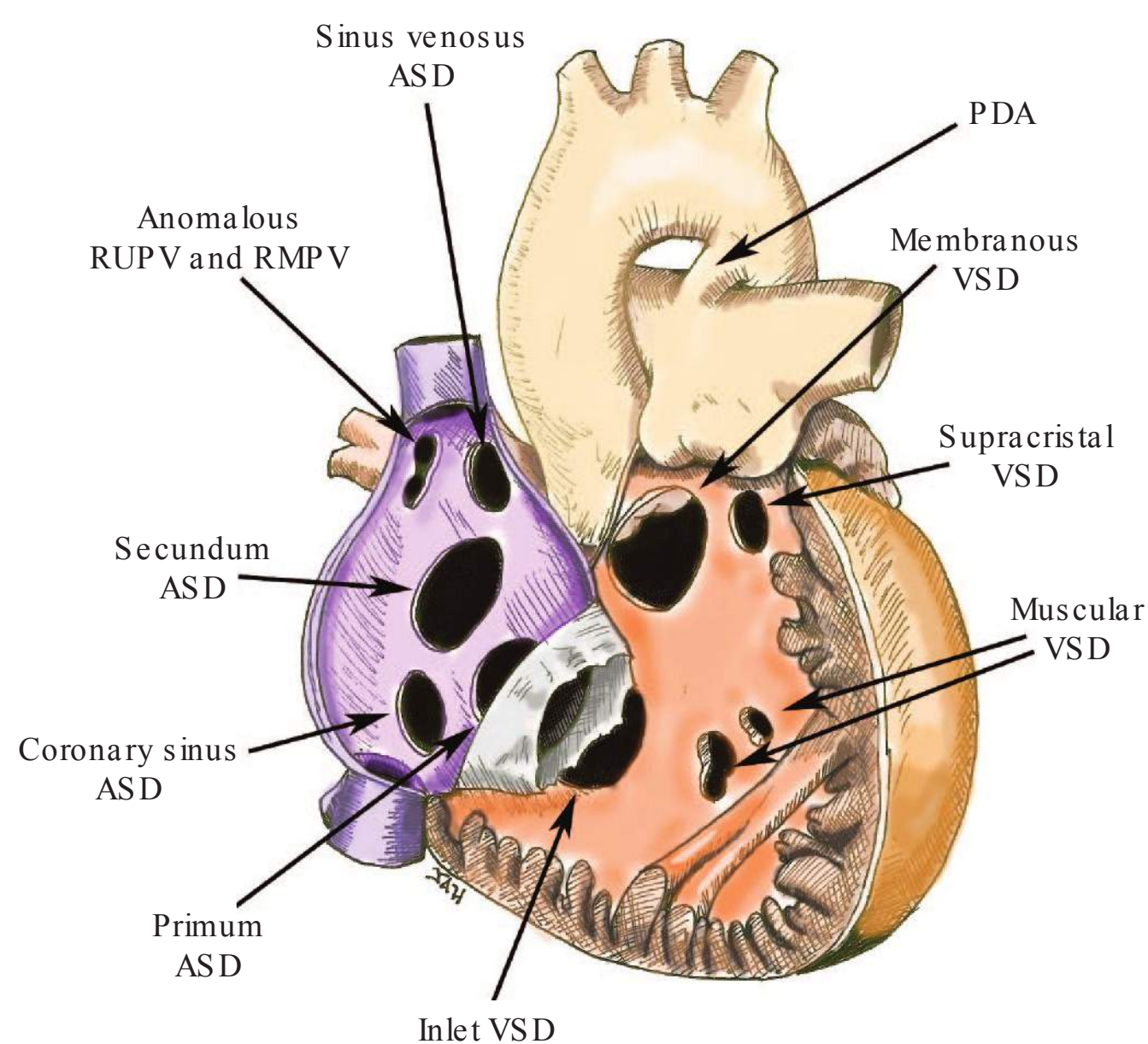


FIGURE 22-1

Types and locations of congenital cardiac defects. ASD, atrial septal defect; PDA, patent ductus arteriosus; RMPV, right middle pulmonary vein; RUPV, right upper pulmonary vein; VSD, ventricular septal defect.

associated mitral or tricuspid regurgitation or a ventricular septal defect (VSD).

These findings are altered when increased pulmonary vascular resistance causes diminution of the left-to-right shunt. Both the pulmonary outflow and tricuspid inflow murmurs decrease in intensity, the pulmonic component of the second heart sound and a systolic ejection sound are accentuated, the two components of the second heart sound may fuse, and a diastolic murmur of pulmonic regurgitation appears. Cyanosis and clubbing accompany the development of a right-to-left shunt (see “Ventricular Septal Defect” later in this chapter). In adults with an ASD and atrial fibrillation, the physical findings may be confused with mitral stenosis with pulmonary hypertension because the tricuspid diastolic flow murmur and widely split second heart sound may be mistakenly thought to represent the diastolic murmur of mitral stenosis and the mitral “opening snap,” respectively.

Electrocardiogram

In ostium secundum ASD, electrocardiogram (ECG) usually shows right-axis deviation and an rSr' pattern in the right precordial leads representing enlargement of the RV outflow tract. An ectopic atrial pacemaker or first-degree heart block may occur with the sinus venous ASD. In ostium primum ASD, the RV conduction defect is accompanied by left superior axis deviation and counterclockwise rotation of the frontal plane QRS loop. Varying degrees of RV and right atrial (RA) enlargement or hypertrophy may occur with each type of defect, depending on the presence and degree of pulmonary hypertension. Chest x-ray shows an enlarged RA and RV, and pulmonary artery and its branches; increased pulmonary vascular markings of left-to-right shunt vascularity will diminish if pulmonary vascular disease develops.

Echocardiogram

Echocardiography reveals pulmonary arterial and RV and RA dilatation with abnormal (paradoxical) ventricular septal motion in the presence of a significant right heart volume overload. The ASD may be visualized directly by two-dimensional imaging, color-flow imaging, or echocontrast. Echocardiography and Doppler examination have supplanted cardiac catheterization. Transesophageal echocardiography is indicated if the transthoracic echocardiogram is ambiguous, which is often the case with sinus venosus defects, or for guiding catheter device closure (**Fig. 22-2**). Cardiac catheterization is performed if inconsistencies exist in the clinical data, if significant pulmonary hypertension or associated malformations are suspected, if CAD is a possibility, or when attempting transcatheter closure of the ASD.

TREATMENT Atrial Septal Defect

Operative repair, usually with a patch of pericardium or of prosthetic material or percutaneous transcatheter device closure, if the ASD is of an appropriate size and shape, should be advised for all patients with uncomplicated secundum ASD with significant left-to-right shunting, i.e., pulmonary-to-systemic flow ratios $\geq 1.5:1$. Excellent results may be anticipated, at low risk, even in patients >40 years, in the absence of severe pulmonary hypertension. In ostium primum ASD, cleft mitral valves may require repair in addition to patch closure of the ASD. Closure is not usually carried out in patients with small defects and trivial left-to-right shunts or in those with severe pulmonary vascular disease without a significant left-to-right shunt. However, the use of pulmonary vasodilators with resultant reduction in pulmonary artery pressure and resistance may allow closure of ASD in patients with pulmonary vascular disease.

Patients with sinus venosus or ostium secundum ASDs rarely die before the fifth decade. During the fifth and sixth decades, the incidence of progressive symptoms, often leading to severe disability, increases substantially. Medical management should include prompt treatment of respiratory tract infections; antiarrhythmic medications for atrial fibrillation or supraventricular tachycardia; and the usual measures for hypertension, coronary disease, or heart failure (**Chap. 19**), if these complications occur. The risk of infective endocarditis is low, and antibiotic prophylaxis is not recommended (**Chap. 31**).

VENTRICULAR SEPTAL DEFECT

VSD is one of the most common of all cardiac birth defects, either as an isolated defect or as a component of a combination of anomalies (**Fig. 22-1**). The VSD is usually single and situated in the membranous or mid-muscular portion of the septum. The functional disturbance depends on its size and on the status of the pulmonary vascular bed. Only small- or moderate-size VSDs are seen initially in adulthood, as most patients with an isolated large VSD come to medical or surgical attention early in life.

A wide spectrum exists in the natural history of VSD, ranging from spontaneous closure to congestive cardiac failure and death in infancy. Included within this spectrum is the possible development of pulmonary vascular obstruction, RV outflow tract obstruction, aortic regurgitation, or infective endocarditis. Spontaneous closure is more common in patients born with a small VSD, which occurs in early childhood in most. The pulmonary vascular bed is often a principal determinant of the clinical manifestations and course of a given VSD and feasibility of surgical repair. Increased pulmonary arterial pressure results from increased pulmonary blood flow and/or resistance, the latter usually the result of obstructive, obliterative structural changes within the

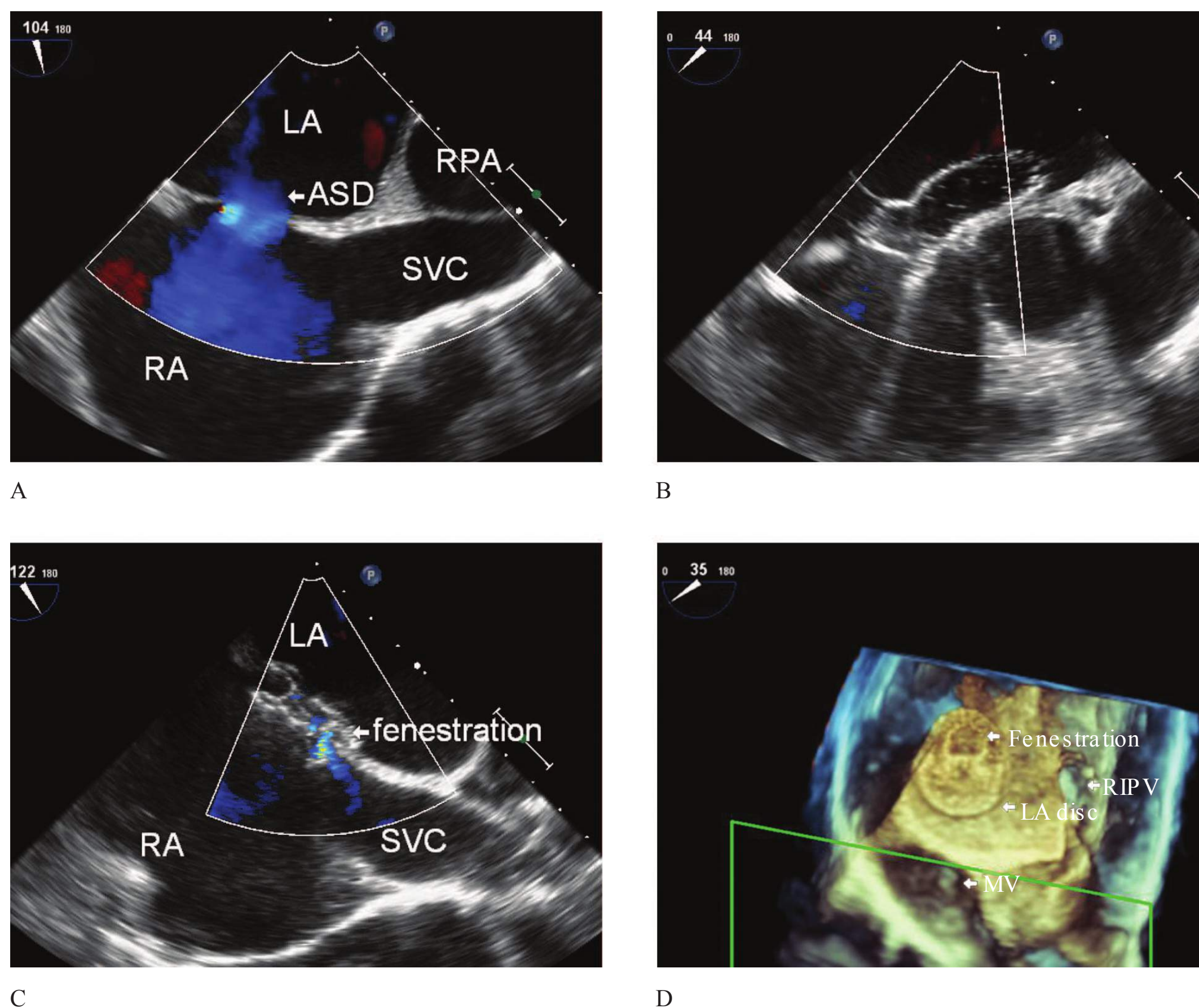


FIGURE 22-2

A. Transesophageal echocardiogram demonstrating a secundum-type atrial septal defect (ASD) with shunting from the left atrium (LA) to the right atrium (RA). The right pulmonary artery (RPA) and superior vena cava (SVC) are labeled. B. Transcatheter balloon sizing of the ASD. C. Atrial septal occluder placement with a small manually created “fenestration” within the device that continues

to allow a small amount of flow from the LA to the RA; this is used as a means of preventing left atrial hypertension after ASD closure. Left atrial hypertension may occur in older patients with decreased left ventricular compliance. D. Three-dimensional image of the septal occluder en-face; note the fenestration in the LA disc. The mitral valve (MV) and right inferior pulmonary vein (RIPV) are labeled.

pulmonary vascular bed. It is important to quantitate and compare pulmonary-to-systemic flows and resistances in patients with severe pulmonary hypertension. The term Eisenmenger’s syndrome is applied to patients with a large communication between the two circulations at the aortopulmonary, ventricular, or atrial levels and bidirectional or predominantly right-to-left shunts because of high resistance and obstructive pulmonary hypertension.

Patients with large VSDs and pulmonary hypertension are at greatest risk for developing pulmonary vascular disease. Large VSDs should be corrected early in life when pulmonary vascular disease is not severely elevated. In patients with Eisenmenger’s syndrome, symptoms in adult life consist of exertional dyspnea, chest pain, syncope, and hemoptysis. The right-to-left shunt leads to cyanosis, clubbing, and erythrocytosis (see below). The degree to which pulmonary vascular resistance is elevated before operation is a critical factor determining prognosis. If the pulmonary vascular

resistance is one-third or less of the systemic value, progression of pulmonary vascular disease after operation is unusual; however, if a moderate to severe increase in pulmonary vascular resistance exists preoperatively, either no change or a progression of pulmonary vascular disease is common postoperatively. Pregnancy is contraindicated in Eisenmenger’s syndrome. The mother’s health is most at risk if she has a cardiovascular lesion associated with pulmonary vascular disease and pulmonary hypertension (e.g., Eisenmenger’s physiology or mitral stenosis) or severe LV outflow tract obstruction (e.g., aortic stenosis), but she is also at risk of death with any malformation that may cause heart failure or a hemodynamically important arrhythmia. The fetus is most at risk with maternal cyanosis, heart failure, or pulmonary hypertension.

RV outflow tract obstruction develops in ~5–10% of patients who present in infancy with a moderate to large left-to-right shunt. With time, as subvalvular RV outflow tract obstruction progresses, the findings in these patients

whose VSD remains sizable begin to resemble more closely those of the cyanotic tetralogy of Fallot. In ~5% of patients, aortic valve regurgitation results from insufficient cusp tissue or prolapse of the cusp through the interventricular defect; the aortic regurgitation then complicates and dominates the clinical course. Echocardiography with spectral and color Doppler examination defines the number and location of defects in the ventricular septum and associated anomalies and the hemodynamic physiology of the defect(s). Hemodynamic and angiographic study may be occasionally required to assess the status of the pulmonary vascular bed and clarify details of the altered anatomy. Cross-sectional imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) are useful in delineating complex anatomy and assessing extracardiac structures.

TREATMENT Ventricular Septal Defect

Closure is not recommended for patients with normal pulmonary arterial pressures with small shunts (pulmonary-to-systemic flow ratios of $<1.5:1$). Operative correction or transcatheter closure is indicated when there is a moderate to large left-to-right shunt with a pulmonary-to-systemic flow ratio $>1.5:1$, in the absence of prohibitively high levels of pulmonary vascular resistance (pulmonary arterial resistance is less than two-thirds of systemic arterial resistance).

In patients with Eisenmenger's VSD, pulmonary arterial vasodilators and both single- or double-lung transplantation with intracardiac defect repair or heart/lung transplantation show promise for improvement in symptoms (**Chap. 21**). Chronic hypoxemia in cyanotic CHD results in secondary erythrocytosis due to increased erythropoietin production (**Chap. 6**). The term polycythemia is a misnomer; white cell counts are normal, and platelet counts are normal to decreased. Compensated erythrocytosis with iron-replete equilibrium hematocrits rarely results in symptoms of hyperviscosity at hematocrits $<65\%$ and occasionally not even with hematocrits $\geq 70\%$. For this reason, therapeutic phlebotomy is rarely required in compensated erythrocytosis. In contrast, patients with decompensated erythrocytosis fail to establish equilibrium with unstable, rising hematocrits and recurrent hyperviscosity symptoms. Therapeutic phlebotomy, a two-edged sword, allows temporary relief of symptoms but limits oxygen delivery, begets instability of the hematocrit, and compounds the problem by iron depletion. Iron-deficiency symptoms are usually indistinguishable from those of hyperviscosity; progressive symptoms after recurrent phlebotomy are usually due to iron depletion with hypochromic microcytosis. Iron depletion results in a larger number of smaller (microcytic) hypochromic

red cells that are less capable of carrying oxygen and less deformable in the microcirculation; with more of them relative to plasma volume, viscosity is greater than for an equivalent hematocrit with fewer, larger, iron-replete, deformable cells. As such, iron-depleted erythrocytosis results in increasing symptoms due to decreased oxygen delivery to the tissues.

Hemostasis is abnormal in cyanotic CHD, due, in part, to the increased blood volume and engorged capillaries, abnormalities in platelet function, and sensitivity to aspirin or nonsteroidal anti-inflammatory agents, as well as abnormalities of the extrinsic and intrinsic coagulation system. Oral contraceptives are often contraindicated for cyanotic women because of the enhanced risk of vascular thrombosis. Symptoms of hyperviscosity can be produced in any cyanotic patient with erythrocytosis if dehydration reduces plasma volume. Phlebotomy for symptoms of hyperviscosity not due to dehydration or iron deficiency is a simple outpatient removal of 500 mL of blood over 45 min with isovolumetric replacement with isotonic saline. Acute phlebotomy without volume replacement is contraindicated. Iron repletion in decompensated iron-depleted erythrocytosis reduces iron-deficiency symptoms, but must be done gradually to avoid an excessive rise in hematocrit and resulting hyperviscosity.

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus is a vessel leading from the bifurcation of the pulmonary artery to the aorta just distal to the left subclavian artery (Fig. 22-1). Normally, the vascular channel is open in the fetus but closes immediately after birth. The flow across the ductus is determined by the pressure and resistance relationships between the systemic and pulmonary circulations and by the cross-sectional area and length of the ductus. In most adults with this anomaly, pulmonary pressures are normal, and a gradient and shunt from aorta to pulmonary artery persist throughout the cardiac cycle, resulting in a characteristic thrill and a continuous "machinery" murmur with late systolic accentuation at the upper left sternal edge. In adults who were born with a large left-to-right shunt through the ductus arteriosus, pulmonary vascular obstruction (Eisenmenger's syndrome) with pulmonary hypertension, right-to-left shunting, and cyanosis have usually developed. Severe pulmonary vascular disease results in reversal of flow through the ductus; unoxygenated blood is shunted to the descending aorta; and the toes—but not the fingers—become cyanotic and clubbed, a finding termed differential cyanosis (Fig. 22-3). The leading causes of death in adults with patent ductus arteriosus are cardiac failure and infective endocarditis; occasionally, severe pulmonary vascular obstruction may cause aneurysmal dilatation, calcification, and rupture of the ductus.

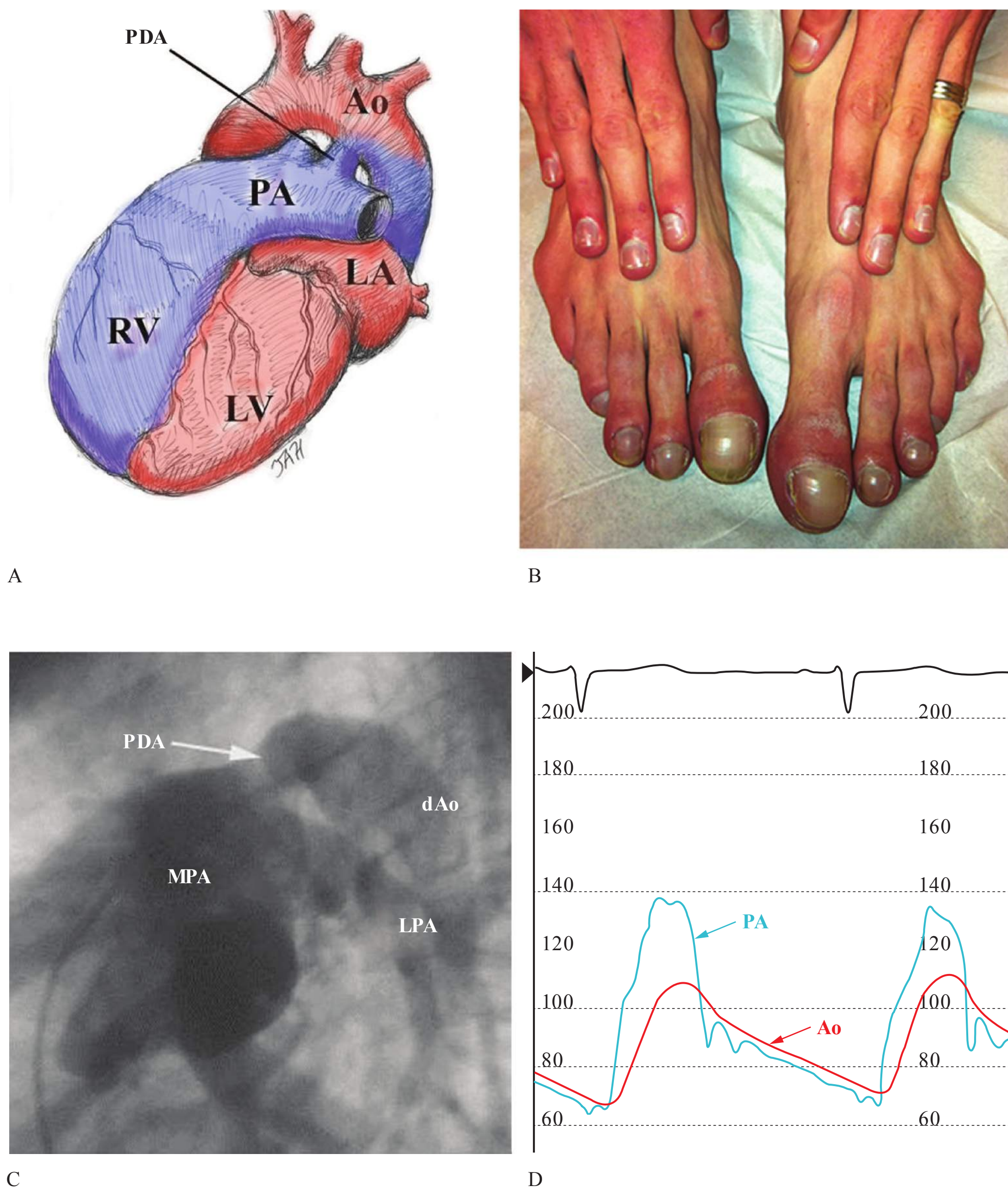


FIGURE 22-3

A. Patent ductus arteriosus (PDA) in a patient with severe pulmonary hypertension (Eisenmenger's syndrome). Due to the suprasystemic pulmonary arterial resistance, deoxygenated (cyanotic) blood from the right ventricle (RV) and pulmonary artery (PA) is shunted across the PDA to the aorta (Ao). The left atrium (LA) and left ventricle (LV) are labeled. B. Differential clubbing and cyanosis

of the toes due to lower extremity perfusion by the deoxygenated blood crossing the PDA. C. Angiogram in a dilated main pulmonary artery (MPA) with shunting noted across the PDA to the descending aorta (dAo). The left pulmonary artery (LPA) is labeled. D. Direct pressure recordings in the Ao and PA demonstrating suprasystemic PA systolic pressure.

TREATMENT Patent Ductus Arteriosus

In the absence of severe pulmonary vascular disease and predominant left-to-right shunting of blood, the patent ductus should be surgically ligated or divided. Transcatheter closure has become common for appropriately shaped defects. Operation should be deferred for several months in patients treated successfully for infective endocarditis because the ductus may remain somewhat edematous and friable.

AORTIC ROOT-TO-RIGHT-HEART SHUNTS

The three most common causes of aortic root-to-right-heart shunts are congenital aneurysm of an aortic sinus of Valsalva with fistula, coronary arteriovenous fistula, and anomalous origin of the left coronary artery from the pulmonary trunk. Aneurysm of an aortic sinus of Valsalva consists of a separation or lack of fusion between the media of the aorta and the annulus of the aortic valve. Rupture usually occurs in the third or fourth decade of life; most often, the aorticocardi-

fistula is between the right coronary cusp and the RV; but occasionally, when the noncoronary cusp is involved, the fistula drains into the RA. Abrupt rupture causes chest pain, bounding pulses, a continuous murmur accentuated in diastole, and volume overload of the heart. Diagnosis is confirmed by two-dimensional and Doppler echocardiographic studies; cardiac catheterization quantitates the left-to-right shunt, and thoracic aortography visualizes the fistula. Medical management is directed at cardiac failure, arrhythmias, or endocarditis. At operation, the aneurysm is closed and amputated, and the aortic wall is reunited with the heart, either by direct suture or with a patch or prosthesis. Transcatheter device closure is a less invasive and effective alternative to surgery.

Coronary arteriovenous fistula, an unusual anomaly, consists of a communication between a coronary artery and another cardiac chamber, usually the coronary sinus, RA, or RV. The shunt is usually of small magnitude, and myocardial blood flow is not usually compromised; if the shunt is large, there may be a coronary “steal” syndrome with myocardial ischemia and possible angina or ventricular arrhythmias. Potential complications include infective endocarditis; thrombus formation with occlusion or distal embolization with myocardial infarction; rupture of an aneurysmal fistula; and, rarely, pulmonary hypertension and congestive failure. A loud, superficial, continuous murmur at the lower or midsternal border usually prompts a further evaluation of asymptomatic patients. Doppler echocardiography demonstrates the site of drainage; if the site of origin is proximal, it may be detectable by two-dimensional echocardiography. Angiography (classic catheterization, CT, or magnetic resonance angiography) permits identification of the size and anatomic features of the fistulous tract, which may be closed by suture or transcatheter obliteration.

The third anomaly causing a shunt from the aortic root to the right heart is anomalous origin of the left coronary artery from the pulmonary artery. In this condition, oxygenated blood from the aortic root flows via a dilated right coronary artery and collaterals to the left coronary artery and retrograde to the lower pressure pulmonary artery circulation via the anomalous left main coronary artery (which emerges from the pulmonary artery). Myocardial infarction and fibrosis commonly lead to death within the first year, although up to 20% of patients survive to adolescence and beyond without surgical correction. The diagnosis is supported by the ECG findings of an anterolateral myocardial infarction and left ventricular hypertrophy (LVH). Operative management of adults consists of coronary artery reimplantation, coronary artery bypass with an internal mammary artery graft, or saphenous vein–coronary artery graft.

CONGENITAL AORTIC STENOSIS

Malformations that cause obstruction to LV outflow include congenital valvular aortic stenosis, discrete subaortic stenosis, or supravulvular aortic stenosis. Bicuspid aortic valves are more common in males than in females. The congenital bicuspid aortic valve, which may initially be functionally normal, is one of the most common congenital malformations of the heart and may go undetected in early life. Because bicuspid valves may develop stenosis or regurgitation with time or be the site of infective endocarditis, the lesion may be difficult to distinguish in older adults from acquired rheumatic or degenerative calcific aortic valve disease. The dynamics of blood flow associated with a congenitally deformed, rigid aortic valve commonly lead to thickening of the cusps and, in later life, to calcification. Hemodynamically significant obstruction causes concentric hypertrophy of the LV wall. The ascending aorta is often dilated, misnamed “poststenotic” dilatation; this is due to histologic abnormalities of the aortic media and may result in aortic dissection. Diagnosis is made by echocardiography, which reveals the morphology of the aortic valve and aortic root and quantitates severity of stenosis or regurgitation. **The clinical manifestations and hemodynamic abnormalities are discussed in Chap. 23.**

TREATMENT Valvular Aortic Stenosis

In patients with diminished cardiac reserve, medical management includes the administration of digoxin and diuretics and sodium restriction while awaiting operation. A dilated aortic root may require beta blockers, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors. Aortic valve replacement is indicated in adults with critical obstruction, i.e., with an aortic valve area $<0.45 \text{ cm}^2/\text{m}^2$, with symptoms secondary to LV dysfunction or myocardial ischemia, or with hemodynamic evidence of LV dysfunction. In asymptomatic children or adolescents or young adults with critical aortic stenosis without valvular calcification or these features, aortic balloon valvuloplasty is often useful (**Chap. 42**). If surgery is contraindicated in older patients because of a complicating medical problem such as malignancy or renal or hepatic failure, balloon valvuloplasty may provide short-term improvement. This procedure may serve as a bridge to aortic valve replacement in patients with severe heart failure. Transcatheter aortic valve replacement is a potential alternative to surgery.

Subaortic stenosis

The discrete form of subaortic stenosis consists of a membranous diaphragm or fibromuscular ring encircling the LV outflow tract just beneath the base of the

aortic valve. The jet impact from the subaortic stenotic jet on the underside of the aortic valve often begets progressive aortic valve fibrosis and valvular regurgitation. Echocardiography demonstrates the anatomy of the subaortic obstruction; Doppler studies show turbulence proximal to the aortic valve and can quantitate the pressure gradient and severity of aortic regurgitation. Treatment consists of complete excision of the membrane or fibromuscular ring.

Supravalvular aortic stenosis

This is a localized or diffuse narrowing of the ascending aorta originating just above the level of the coronary arteries at the superior margin of the sinuses of Valsalva. In contrast to other forms of aortic stenosis, the coronary arteries are subjected to elevated systolic pressures from the LV, are often dilated and tortuous, and are susceptible to premature atherosclerosis. The coronary ostia may also become obstructed by the aortic valve leaflets. In most patients, a genetic defect for the anomaly is located in the same chromosomal region as elastin on chromosome 7. Supravalvular aortic stenosis is the most commonly associated cardiac defect in Williams-Beuren syndrome, typically comprising the following: “elfin” facies, low nasal bridge, cheerful demeanor, mental retardation with retained language skills and love of music, supravalvular aortic stenosis, and transient hypercalcemia.

COARCTATION OF THE AORTA

Narrowing or constriction of the lumen of the aorta may occur anywhere along its length but is most common distal to the origin of the left subclavian artery near the insertion of the ligamentum arteriosum. Coarctation occurs in ~7% of patients with CHD, is more common in males than females, and is particularly frequent in patients with gonadal dysgenesis (e.g., Turner’s syndrome). Clinical manifestations depend on the site and extent of obstruction and the presence of associated cardiac anomalies, most commonly a bicuspid aortic valve. Circle of Willis aneurysms may occur in up to 10%.

Most children and young adults with isolated, discrete coarctation are asymptomatic. Headache, epistaxis, chest pressure, and claudication with exercise may occur, and attention is usually directed to the cardiovascular system when a heart murmur or hypertension in the upper extremities and absence, marked diminution, or delayed pulsations in the femoral arteries are detected on physical examination. Enlarged and pulsatile collateral vessels may be palpated in the intercostal spaces anteriorly, in the axillae, or posteriorly in the interscapular area. The upper extremities and thorax may be more developed than the lower extremities. A midsystolic murmur over the left interscapular space

may become continuous if the lumen is narrowed sufficiently to result in a high-velocity jet across the lesion throughout the cardiac cycle. Additional systolic and continuous murmurs over the lateral thoracic wall may reflect increased flow through dilated and tortuous collateral vessels. The ECG usually reveals LV hypertrophy. Chest x-ray may show a dilated left subclavian artery high on the left mediastinal border and a dilated ascending aorta. Indentation of the aorta at the site of coarctation and pre- and poststenotic dilatation (the “3” sign) along the left paramediastinal shadow are essentially pathognomonic. Notching of the third to ninth ribs, an important radiographic sign, is due to inferior rib erosion by dilated collateral vessels. Two-dimensional echocardiography from suprasternal windows identifies the site of coarctation; Doppler quantitates the pressure gradient. Transesophageal echocardiography and MRI or CT allow visualization of the length and severity of the obstruction and associated collateral arteries. In adults, cardiac catheterization is indicated primarily to evaluate the coronary arteries or to perform catheter-based intervention (angioplasty and stent of the coarctation).

The chief hazards of proximal aortic severe hypertension include cerebral aneurysms and hemorrhage, aortic dissection and rupture, premature coronary arteriosclerosis, aortic valve failure, and LV failure; infective endarteritis may occur on the coarctation site or endocarditis may settle on an associated bicuspid aortic valve, which is estimated to be present in 50% of patients.

TREATMENT Coarctation of the Aorta

Treatment is surgical or involves percutaneous catheter balloon dilatation with stent placement; the details of selection of therapy are beyond this review; however, the use of transcatheter treatment techniques has increased dramatically, and many previously “surgical” cases are treated via percutaneous or hybrid techniques. Late postoperative systemic hypertension in the absence of residual coarctation is related partly to the duration of preoperative hypertension. Follow-up of rest and exercise blood pressures is important; many have systolic hypertension only during exercise, in part due to a diffuse vasculopathy and to noncompliance of the stented or surgically reconstructed region. All operated or stented coarctation patients deserve a high-quality MRI or CT procedure in follow-up.

PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

Obstruction to RV outflow may be localized to the supravalvular, valvular, or subvalvular levels or occur at a combination of these sites. Multiple sites of narrowing of the peripheral pulmonary arteries are a feature

of rubella embryopathy and may occur with both the familial and sporadic forms of supra-ventricular aortic stenosis. Valvular pulmonic stenosis (PS) is the most common form of isolated RV obstruction.

The severity of the obstructing lesion, rather than the site of narrowing, is the most important determinant of the clinical course. In the presence of a normal cardiac output, a peak systolic pressure gradient <30 mmHg indicates mild PS and >50 mmHg indicates severe PS; pressures between these limits are considered to indicate moderate stenosis. Patients with mild PS are generally asymptomatic and demonstrate little or no progression in the severity of obstruction with age. In patients with more significant stenosis, the severity may increase with time. Symptoms vary with the degree of obstruction. Fatigue, dyspnea, RV failure, and syncope may limit the activity of older patients, in whom moderate or severe obstruction may prevent an augmentation of cardiac output with exercise. In patients with severe obstruction, the systolic pressure in the RV may exceed that in the LV, because the ventricular septum is intact. RV ejection is prolonged with moderate or severe stenosis, and the sound of pulmonary valve closure is delayed and soft. RV hypertrophy reduces the compliance of that chamber, and a forceful RA contraction is necessary to augment RV filling. A fourth heart sound; prominent a waves in the jugular venous pulse; and, occasionally, presystolic pulsations of the liver reflect vigorous atrial contraction. The clinical diagnosis is supported by a left parasternal lift and harsh systolic crescendo-decrescendo murmur and thrill at the upper left sternal border, typically preceded by a systolic ejection sound if the obstruction is due to a mobile non-dysplastic pulmonary valve. The holosystolic murmur of tricuspid regurgitation may accompany severe PS, especially in the presence of congestive heart failure. Cyanosis usually reflects right-to-left shunting through a patent foramen ovale or ASD. In patients with supra-ventricular or peripheral pulmonary arterial stenosis, the murmur is systolic or continuous and is best heard over the area of narrowing, with radiation to the peripheral lung fields.

In mild cases, the ECG is normal, whereas moderate and severe stenoses are associated with RV hypertrophy. The chest x-ray with mild or moderate PS shows a heart of normal size with normal lung vascularity. In pulmonary valvular stenosis, dilatation of the main and left pulmonary arteries occurs in part due to the direction of the PS jet and in part due to intrinsic tissue weakness. With severe obstruction, RV hypertrophy is generally evident. The pulmonary vascularity may be reduced with severe stenosis, RV failure, and/or a right-to-left shunt at the atrial level. Two- and three-dimensional echocardiography visualizes pulmonary valve morphology; the outflow tract pressure

gradient is quantitated by Doppler echocardiography (Fig. 22-4).

TREATMENT PULMONARY STENOSIS

The cardiac catheter technique of balloon valvuloplasty (Chap. 13) is usually effective, and the surgery is rarely necessary. Multiple stenoses of the peripheral pulmonary arteries are effectively treated with transcatheter angioplasty or stenting.

TETRALOGY OF FALLOT

The four components of the tetralogy of Fallot are malaligned VSD, obstruction to RV outflow, aortic override of the VSD, and RV hypertrophy due to the RV's response to aortic pressure via the large VSD.

The severity of RV outflow obstruction determines the clinical presentation. The severity of hypoplasia of the RV outflow tract varies from mild to complete (pulmonary atresia). Pulmonary valve stenosis and supra-ventricular and peripheral pulmonary arterial obstruction may coexist; rarely, there is unilateral absence of a pulmonary artery (usually the left). A right-sided aortic arch and descending thoracic aorta occur in ~25%.

The relationship between the resistance of blood flow from the ventricles into the aorta and into the pulmonary artery plays a major role in determining the hemodynamic and clinical picture. When the RV outflow obstruction is severe, pulmonary blood flow is reduced markedly, and a large volume of desaturated systemic venous blood shunts right-to-left across the VSD. Severe cyanosis and erythrocytosis occur, and symptoms of systemic hypoxemia are prominent. In many infants and children, the obstruction is mild but progressive.

The ECG shows RV hypertrophy. Chest x-ray shows a normal-sized, boot-shaped heart (*coeur en sabot*) with a prominent RV and a concavity in the region of the pulmonary conus. Pulmonary vascular markings are typically diminished, and the aortic arch and knob may be on the right side. Echocardiography demonstrates the malaligned VSD with the overriding aorta and the site and severity of PS, which may be subpulmonic (fixed or dynamic), at the pulmonary valve or in the main or branch pulmonary arteries. Classic contrast angiography may provide details regarding the RV outflow tract, pulmonary valve and annulus, and caliber of the main branches of the pulmonary artery, as well as about possible associated aortopulmonary collaterals. Coronary arteriography identifies the anatomy and course of the coronary arteries, which may be anomalous. Cardiac MRI and CT complement echocardiography and provide much of the information gathered by angiography as well as additional functional information. MRI is

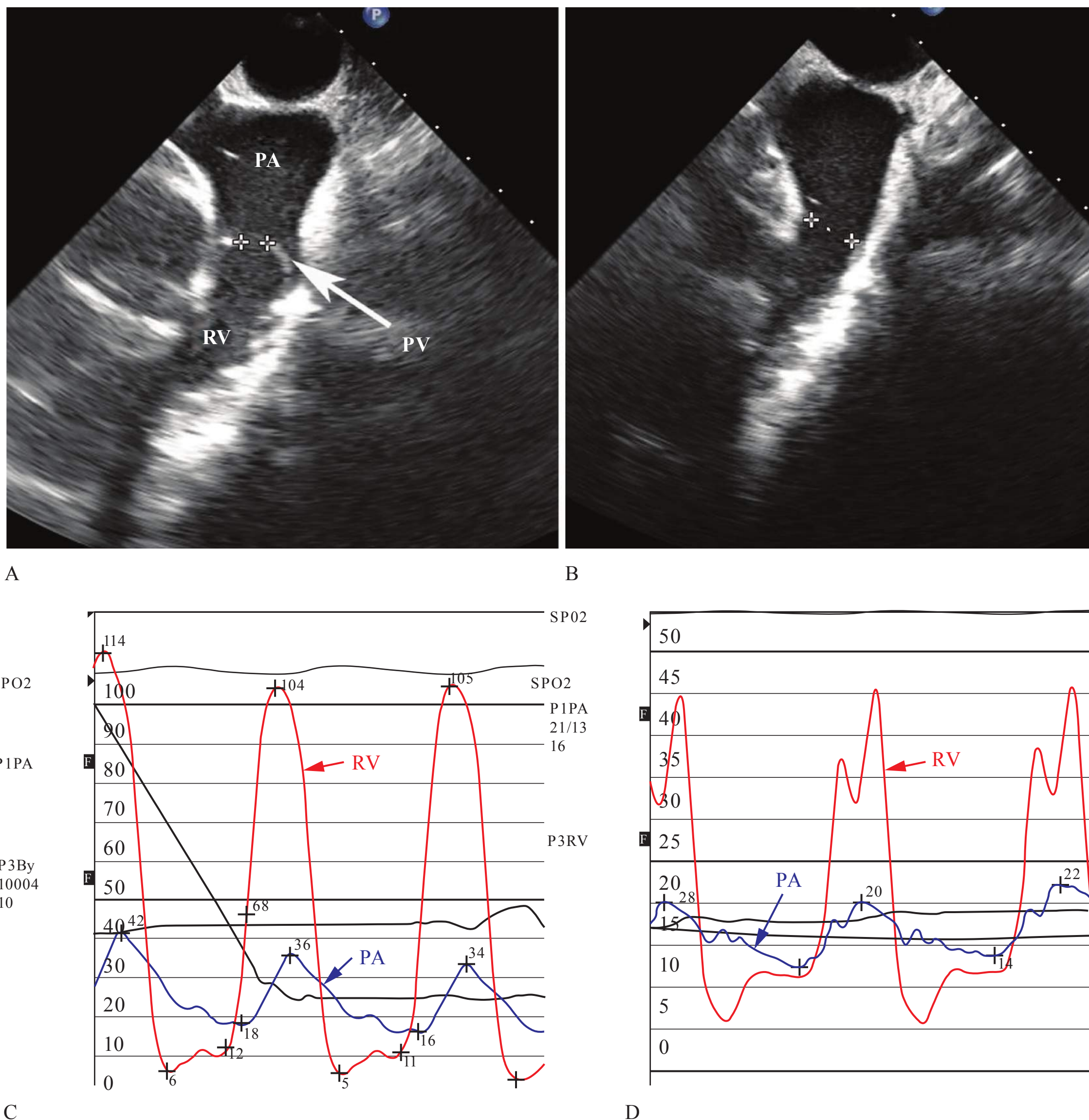


FIGURE 22-4

A. Transesophageal echocardiogram of a patient with severe pulmonary stenosis due to a mobile and doming pulmonary valve (PV). The pulmonary artery (PA) and the right ventricle (RV) are labeled. B. Following balloon valvuloplasty, the pulmonary valve

orifice is larger. C. Simultaneous RV and PA pressure tracings before balloon valvuloplasty; the peak-to-peak gradient across the pulmonary valve is ~70 mmHg. D. After balloon valvuloplasty, the peak-to-peak gradient is reduced to ~25 mmHg.

considered the clinical gold standard for quantification of RV volume and function as well as quantification of the pulmonary regurgitation severity.

TREATMENT Tetralogy of Fallot

For a variety of reasons, only a few adults with tetralogy of Fallot have not had some form of previous surgical intervention. Reoperation in adults is most commonly for severe pulmonary regurgitation or pulmonary stenosis. Long-term concerns about ventricular function persist. Ventricular and atrial arrhythmias occur, respectively, in 15% and 25% of adults and may require medical treatment, electrophysiologic

study and ablation, defibrillator placement, or transcatheter or surgical intervention, usually including pulmonary valve replacement. Transcatheter pulmonary valve replacement is widely used in patients meeting anatomic criteria. The aortic root has a medial tissue defect; it is commonly enlarged and associated with aortic regurgitation. Endocarditis remains a risk despite surgical repair.

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

This condition is commonly called dextro- or d-transposition of the great arteries. The aorta arises rightward anteriorly from the RV, and the pulmonary artery emerges

leftward and posteriorly from the LV, which results in two separate parallel circulations; some communication between them must exist after birth to sustain life. Most patients have an interatrial communication, two-thirds have a patent ductus arteriosus, and about one-third have an associated VSD. Transposition is more common in males and accounts for ~10% of cyanotic heart disease. The course is determined by the degree of tissue hypoxemia, the ability of each ventricle to sustain an increased workload in the presence of reduced coronary arterial oxygenation, the nature of the associated cardiovascular anomalies, and the status of the pulmonary vascular bed. Patients who do not undergo surgical palliation generally do not survive to reach adulthood. The long-term outcomes in those that have undergone surgery are in large part determined by the type of surgery performed. By the third decade of life, ~30% of patients with “atrial switch” operations will have developed decreased RV function and progressive tricuspid regurgitation, which may lead to congestive heart failure. Pulmonary vascular obstruction develops by 1–2 years of age in patients with an associated large VSD or large patent ductus arteriosus in the absence of obstruction to LV outflow.

TREATMENT Transposition of the Great Arteries

The balloon or blade catheter or surgical creation or enlargement of an interatrial communication in the neonate is the simplest procedure for providing increased intracardiac mixing of systemic and pulmonary venous blood. Systemic pulmonary artery anastomosis may be indicated in the patient with severe obstruction to LV outflow and diminished pulmonary blood flow. Intracardiac repair may be accomplished by rearranging the venous returns (intraatrial switch, i.e., Mustard or Senning operation) so that the systemic venous blood is directed to the mitral valve and, thence, to the LV and pulmonary artery, while the pulmonary venous blood is diverted through the tricuspid valve and RV to the aorta. The late survival after these repairs is good, but arrhythmias (e.g., atrial flutter) or conduction defects (e.g., sick sinus syndrome) occur in ~50% of such patients by 30 years after the intraatrial switch surgery. Progressive dysfunction of the systemic subaortic RV, tricuspid regurgitation, ventricular arrhythmias, cardiac arrest, and late sudden death are worrisome features. Preferably, this malformation is corrected in infancy by transposing both coronary arteries to the posterior artery and transecting, contraposing, and anastomosing the aorta and pulmonary arteries (arterial-switch operation). For patients with a VSD in whom it is necessary to bypass a severely obstructed LV outflow tract, corrective operation employs an intracardiac ventricular baffle and extracardiac prosthetic conduit to replace the pulmonary artery (Rastelli procedure).

SINGLE VENTRICLE

This is a family of complex lesions with both atrioventricular valves or a common atrioventricular valve opening to a single ventricular chamber. Associated anomalies include abnormal great artery positional relationships, pulmonic valvular or subvalvular stenosis, and subaortic stenosis. Survival to adulthood depends on a relatively normal pulmonary blood flow, yet normal pulmonary resistance and good ventricular function. Modifications of the Fontan approach are generally applied to carefully selected patients with creation of a pathway(s) from the systemic veins to the pulmonary arteries.

TRICUSPID ATRESIA

This malformation is characterized by atresia of the tricuspid valve; an interatrial communication; and, frequently, hypoplasia of the RV and pulmonary artery. The clinical picture is usually dominated by severe cyanosis due to obligatory admixture of systemic and pulmonary venous blood in the LV. The ECG characteristically shows RA enlargement, left-axis deviation, and LV hypertrophy.

Atrial septostomy and palliative operations to increase pulmonary blood flow, often by anastomosis of a systemic artery or vein to a pulmonary artery, may allow survival to the second or third decade. A Fontan atriopulmonary or total cavopulmonary connection may then allow functional correction in patients with normal or low pulmonary arterial resistance pressure and good LV function. There are a number of important long-term considerations with the Fontan circulation, including the development of arrhythmias, progressive liver dysfunction, thromboembolic complications, and potential long-term need for heart or heart and liver transplantation.

EBSTEIN'S ANOMALY

Characterized by a downward displacement of the tricuspid valve into the RV, due to anomalous attachment of the tricuspid leaflets, the Ebstein tricuspid valve tissue is dysplastic and results in tricuspid regurgitation. The abnormally situated tricuspid orifice produces an “atrialized” portion of the RV lying between the atrioventricular ring and the origin of the valve, which is continuous with the RA chamber. Often, the RV is hypoplastic. Although the clinical manifestations are variable, some patients come to initial attention because of either (1) progressive cyanosis from right-to-left atrial shunting, (2) symptoms due to tricuspid regurgitation and RV dysfunction, or (3) paroxysmal atrial tachyarrhythmias with or without atrioventricular bypass tracts

(Wolff-Parkinson-White [WPW] syndrome). Diagnostic findings by two-dimensional echocardiography include the abnormal positional relation between the tricuspid and mitral valves with abnormally increased apical displacement of the septal tricuspid leaflet. Tricuspid regurgitation is quantitated by Doppler examination. Surgical approaches include prosthetic replacement of the tricuspid valve when the leaflets are tethered or repair of the native valve.

CONGENITALLY CORRECTED TRANSPOSITION

The two fundamental anatomic abnormalities in this malformation are transposition of the ascending aorta and pulmonary trunk and inversion of the ventricles. This arrangement results in desaturated systemic venous blood passing from the RA through the mitral valve to the LV and into the pulmonary trunk, whereas oxygenated pulmonary venous blood flows from the left atrium through the tricuspid valve to the RV and into the aorta. Thus, the circulation is corrected functionally. The clinical presentation, course, and prognosis of patients with congenitally corrected transposition vary depending on the nature and severity of any complicating intracardiac anomalies and of development of dysfunction of the systemic subaortic RV. Progressive RV dysfunction and tricuspid regurgitation may also develop in one-third of patients by age 30; Ebstein-type anomalies of the left-side tricuspid atrioventricular valve are common. VSD or PS due to obstruction to outflow from the right-sided subpulmonary (anatomic left) ventricle may coexist. Complete heart block occurs at a rate of 2–10% per decade. The diagnosis of the malformation and associated lesions can be established by comprehensive two-dimensional echocardiography and Doppler examination.

MALPOSITIONS OF THE HEART

Positional anomalies refer to conditions in which the cardiac apex is in the right side of the chest (dextrocardia) or at the midline (mesocardia), or in which there is a normal location of the heart in the left side of the chest but abnormal position of the viscera (isolated levocardia). Knowledge of the position of the abdominal organs and of the branching pattern of the main stem bronchi is important in categorizing these malpositions. When dextrocardia occurs without situs inversus, when the visceral situs is indeterminate, or if isolated levocardia is present, associated, often complex, multiple cardiac anomalies are usually present. In contrast, mirror-image dextrocardia is usually observed with complete situs inversus, which occurs most frequently in individuals whose hearts are otherwise normal.

SURGICALLY MODIFIED CONGENITAL HEART DISEASE

Owing to the enormous strides in cardiovascular surgical techniques that have occurred in the past 70 years, a large number of long-term survivors of palliative or corrective operations in infancy and childhood have reached adulthood. These patients are often challenging because of the diversity of anatomic, hemodynamic, and electrophysiologic residua and sequelae of cardiac operations.

The proper care of the survivor of an operation for CHD requires that the clinician understand the details of the malformation before operation; pay meticulous attention to the details of the operative procedure; and recognize the postoperative residua (conditions left totally or partially uncorrected), the sequelae (conditions caused by surgery), and the complications that may have resulted from the operation. Except for ligation of an uncomplicated patent ductus arteriosus, almost every other surgical repair leaves behind or causes some abnormality of the heart and circulation that may range from trivial to serious. Thus, even with results that are considered clinically to be good to excellent, continued long-term postoperative follow-up is advisable.

Cardiac operations involving the atria, such as closure of ASD, repair of total or partial anomalous pulmonary venous return, or venous switch corrections of complete transposition of the great arteries (the Mustard or Senning operations), may be followed years later by sinus node or atrioventricular node dysfunction and/or by atrial arrhythmias (especially atrial flutter). Intraventricular surgery may also result in electrophysiologic consequences, including complete heart block necessitating pacemaker insertion to avoid sudden death. Valvular problems may arise late after initial cardiac operation. An example is the progressive stenosis of an initially nonobstructive bicuspid aortic valve in the patient who underwent aortic coarctation repair. Such aortic valves may also be the site of infective endocarditis. After repair of the ostium primum ASD, the cleft mitral valve may become progressively regurgitant. Tricuspid regurgitation may also be progressive in the postoperative patient with tetralogy of Fallot if RV outflow tract obstruction was not relieved adequately at initial surgery. In many patients with surgically modified CHD, inadequate relief of an obstructive lesion, a residual regurgitant lesion, or a residual shunt will cause or hasten the onset of clinical signs and symptoms of myocardial dysfunction. Despite a good hemodynamic repair, many patients with a subaortic RV develop RV decompensation and signs of left heart failure. In many patients, particularly those who were cyanotic for many years before operation, a preexisting compromise in ventricular performance is due to the original underlying malformation.

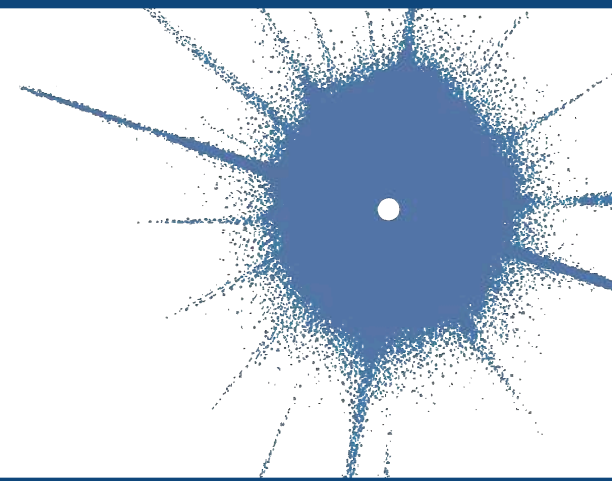
A final category of postoperative problems involves the use of prosthetic valves, patches, or conduits in the operative repair. The special risks include infective endocarditis, thrombus formation, and premature degeneration and calcification of the prosthetic materials. There are many patients in whom extracardiac conduits are required to correct the circulation functionally and often to carry blood to the lungs from the RA or RV. These conduits may develop intraluminal obstruction, and if they include a prosthetic valve, it may show progressive calcification and thickening. Many such patients face reintervention (interventional cardiac catheterization or surgical reoperation) one or more times in their lives. Such care should be directed to centers specializing in adults with complex congenital cardiovascular malformations. The effect of pregnancy in postoperative patients depends on the outcome of the repair, including the presence and severity of residua, sequelae, or complications. Contraception is an important topic with such patients. Tubal ligation should be considered in those in whom pregnancy is strictly contraindicated.

Endocarditis prophylaxis

Two major predisposing causes of infective endocarditis are a susceptible cardiovascular substrate and a source of bacteremia. The clinical and bacteriologic profile of infective endocarditis in patients with CHD has changed with the advent of intracardiac surgery and of prosthetic devices. Prophylaxis includes both antimicrobial and hygienic measures. Meticulous dental and skin care are required. Routine antimicrobial prophylaxis is recommended for bacteremic dental procedures or instrumentation through an infected site in most patients with operated CHD, particularly if foreign material, such as a prosthetic valve, conduit, or surgically constructed shunt, is in place. In the case of patches, in the absence of a high-pressure patch leak, or transcatheter devices, prophylaxis is usually recommended for 6 months until there is endothelialization. Individuals with unrepaired cyanotic heart disease are also generally recommended to receive prophylaxis (**Chap. 31**).

CHAPTER 23

AORTIC VALVE DISEASE



Patrick T. O’Gara ■ Joseph Loscalzo

GLOBAL BURDEN OF VALVULAR HEART DISEASE



Primary valvular heart disease ranks well below coronary heart disease, stroke, hypertension, obesity, and diabetes as a major threat to the public health. Nevertheless, it is the source of significant morbidity and mortality rates. Rheumatic fever (**Chap. 32**) is the dominant cause of valvular heart disease in developing and low-income countries. Its prevalence has been estimated to range from as low as 1 per 100,000 school-age children in Costa Rica to as high as 150 per 100,000 in China. Rheumatic heart disease accounts for 12–65% of hospital admissions related to cardiovascular disease and 2–10% of hospital discharges in some developing countries. Prevalence and mortality rates vary among communities even within the same country as a function of overcrowding and the availability of medical resources and population-wide programs for detection and treatment of group A streptococcal pharyngitis. In economically deprived areas, tropical and subtropical climates (particularly on the Indian subcontinent), Central America, and the Middle East, rheumatic valvular disease progresses more rapidly than in more-developed nations and frequently causes serious symptoms in patients younger than 20 years of age. The accelerated natural history may be due to repeated infections with more virulent strains of rheumatogenic streptococci. Approximately 15 million to 20 million people live with rheumatic heart disease worldwide, an estimated prevalence characterized by 300,000 new cases and 233,000 case fatalities per year, with the highest mortality rates reported from Southeast Asia (~7.6 per 100,000).

Although there have been recent reports of isolated outbreaks of streptococcal infection in North America, valve disease in high-income countries is dominated by degenerative or inflammatory processes that lead

to valve thickening, calcification, and dysfunction. The prevalence of valvular heart disease increases with age for both men and women. Important left-sided valve disease may affect as many as 12–13% of adults older than the age of 75. In the United States, there were 85,000 hospital discharges with valvular heart disease in 2010, and the vast majority of these were related to surgical procedures for heart valve disease (mostly involving the aortic and mitral valves).

The incidence of infective endocarditis (**Chap. 31**) has increased with the aging of the population, the more widespread prevalence of vascular grafts and intracardiac devices, the emergence of more virulent multidrug-resistant microorganisms, and the growing epidemic of diabetes. The more restricted use of antibiotic prophylaxis since 2007 has thus far not been associated with an increase in incidence rates. Infective endocarditis has become a relatively more frequent cause of acute valvular regurgitation.

Bicuspid aortic valve disease affects as many as 0.5–1.4% of the general population, with an associated incidence of aortopathy involving root or ascending aortic aneurysm disease or coarctation. An increasing number of childhood survivors of congenital heart disease present later in life with valvular dysfunction. The global burden of valvular heart disease is expected to progress.

As is true for many other chronic health conditions, disparities in access to and quality of care for patients with valvular heart disease have been well documented. Management decisions and outcome differences based on age, gender, race, and geography require educational efforts across all levels of providers.

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in **Chaps. 9 and 10**; of electrocardiography (ECG) in **Chap. 11**; of echocardiography and other noninvasive imaging techniques in **Chap. 12**; and of cardiac catheterization and angiography in **Chap. 13**.

AORTIC STENOSIS

Aortic stenosis (AS) occurs in about one-fourth of all patients with chronic valvular heart disease; approximately 80% of adult patients with symptomatic, valvular AS are male.

ETIOLOGY AND PATHOGENESIS

(Table 23-1) AS in adults is due to degenerative calcification of the aortic cusps and occurs most commonly on a substrate of congenital disease (bicuspid aortic valve), chronic (trileaflet) deterioration, or previous rheumatic inflammation. A pathologic study of specimens removed at the time of aortic valve replacement for AS showed that 53% were bicuspid and 4% unicuspid. The process of aortic valve deterioration and calcification is not a passive one, but rather one that shares many features with vascular atherosclerosis, including endothelial dysfunction, lipid accumulation, inflammatory cell activation, cytokine release, and upregulation of several signaling pathways (Fig. 23-1). Eventually, valvular myofibroblasts differentiate phenotypically into osteoblasts and actively produce bone matrix proteins that allow for the deposition of calcium hydroxyapatite crystals. Genetic polymorphisms involving the vitamin D receptor, the estrogen receptor in postmenopausal women, interleukin 10, and apolipoprotein E4 have been linked to the development of calcific AS, and a strong familial clustering of cases has been reported

TABLE 23-1

MAJOR CAUSES OF AORTIC VALVE DISEASE	
VALVE LESION	ETIOLOGIES
Aortic stenosis	Congenital (bicuspid, unicuspid)
	Degenerative calcific
	Rheumatic fever
	Radiation
Aortic regurgitation	Valvular
	Congenital (bicuspid)
	Endocarditis
	Rheumatic fever
	Myxomatous (prolapse)
	Traumatic
	Syphilis
	Ankylosing spondylitis
	Root disease
	Aortic dissection
	Cystic medial degeneration
	Marfan's syndrome
	Bicuspid aortic valve
	Nonsyndromic familial aneurysm
	Aortitis
	Hypertension

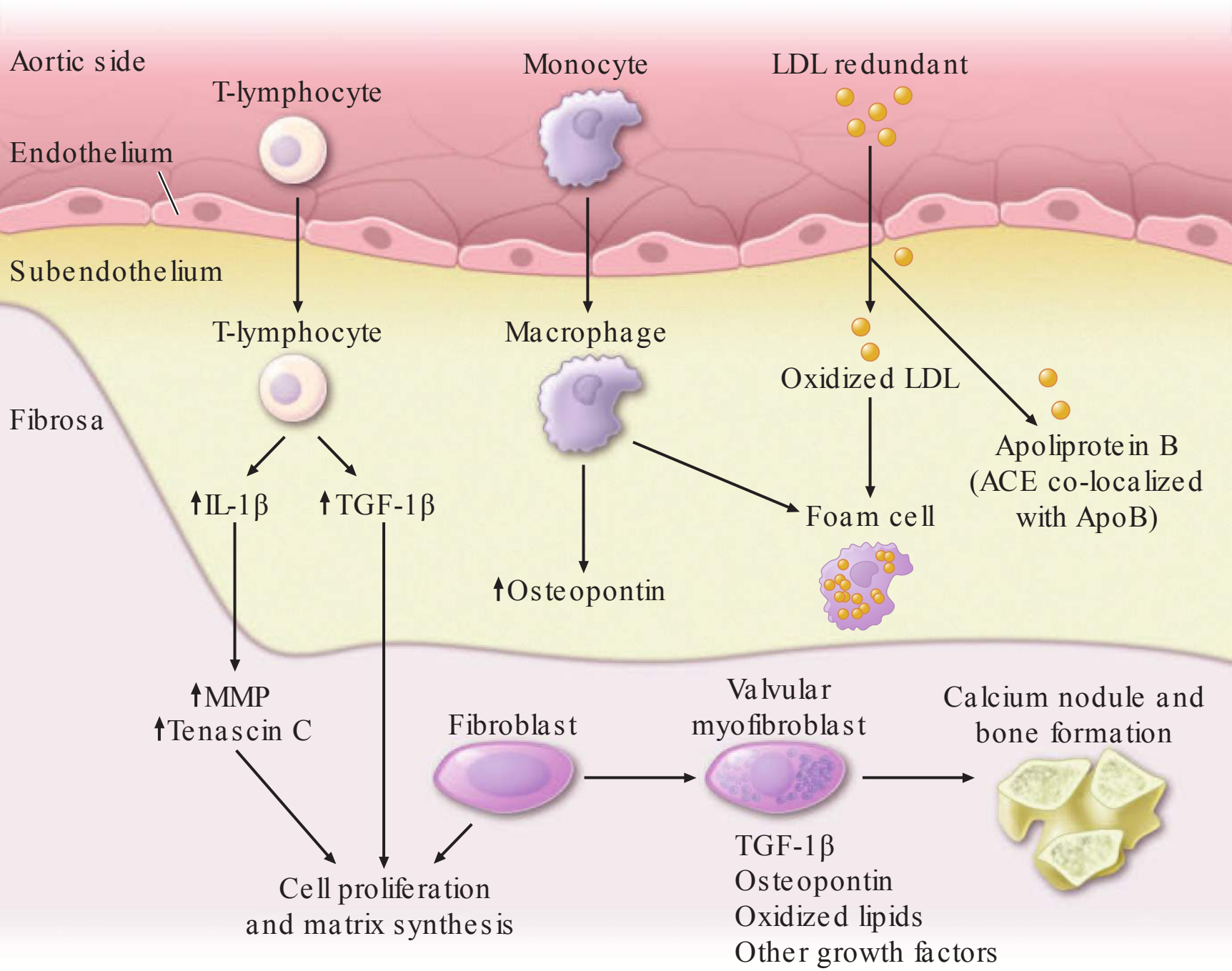


FIGURE 23-1 Pathogenesis of calcific aortic stenosis. Inflammatory cells infiltrate across the endothelial barrier and release cytokines that act on fibroblasts to promote cellular proliferation and matrix remodeling. LDL is oxidatively modified and taken up by macrophage scavengers to become foam cells. Angiotensin-converting enzyme colocalizes with ApoB. A subset of myofibroblasts differentiates into an osteoblast phenotype capable of promoting bone formation. ACE, angiotensin-converting enzyme; ApoB, apolipoprotein B; LDL, low-density lipoprotein; IL, interleukin; MMP, matrix metalloproteinase; TGF, transforming growth factor. (From RV Freeman, CM Otto: Circulation 111:3316, 2005; with permission.)

from western France. Several traditional atherosclerotic risk factors have also been associated with the development and progression of calcific AS, including low-density lipoprotein (LDL) cholesterol, lipoprotein a (Lp[a]), diabetes mellitus, smoking, chronic kidney disease, and the metabolic syndrome. The presence of aortic valve sclerosis (focal thickening and calcification of the leaflets not severe enough to cause obstruction) is associated with an excess risk of cardiovascular death and myocardial infarction (MI) among persons older than age 65. Approximately 30% of persons older than 65 years exhibit aortic valve sclerosis, whereas 2% exhibit frank stenosis.

Rheumatic disease of the aortic leaflets produces commissural fusion, sometimes resulting in a bicuspid-appearing valve. This condition, in turn, makes the leaflets more susceptible to trauma and ultimately leads to fibrosis, calcification, and further narrowing. By the time the obstruction to left ventricular (LV) outflow causes serious clinical disability, the valve is usually a rigid calcified mass, and careful examination may make it difficult or even impossible to determine the etiology of the underlying process. Rheumatic AS is almost always associated with involvement of the mitral valve and with aortic regurgitation. Mediastinal radiation can also result in late scarring, fibrosis, and calcification of the leaflets with AS.

BICUSPID AORTIC VALVE DISEASE

A bicuspid aortic valve (BAV) is the most common congenital heart valve defect and occurs in 0.5–1.4% of the population with a 2–4:1 male-to-female predominance. The inheritance pattern appears to be autosomal dominant with incomplete penetrance, although some have questioned an X-linked component as suggested by the prevalence of BAV disease among patients with Turner's syndrome. The prevalence of BAV disease among first-degree relatives of an affected individual is approximately 10%. A single gene defect to explain the majority of cases has not been identified, although a mutation in the NOTCH1 gene has been described in some families. Abnormalities in endothelial nitric oxide synthase and NKX2.5 have been implicated as well. Medial degeneration with ascending aortic aneurysm formation occurs commonly among patients with BAV disease; aortic coarctation is less frequently encountered. Patients with BAV disease have larger aortas than patients with comparable tricuspid aortic valve disease. The aortopathy develops independent of the hemodynamic severity of the valve lesion and is a risk factor for aneurysm formation and/or dissection. A BAV can be a component of more complex congenital heart disease with or without other left heart obstructing lesions, as seen in Shone's complex.

OTHER FORMS OF OBSTRUCTION TO LEFT VENTRICULAR OUTFLOW

In addition to valvular AS, three other lesions may be responsible for obstruction to LV outflow: hypertrophic obstructive cardiomyopathy (**Chap. 27**), discrete fibromuscular/membranous subaortic stenosis, and supraventricular AS (**Chap. 22**). The causes of LV outflow obstruction can be differentiated on the basis of the cardiac examination and Doppler echocardiographic findings.

PATHOPHYSIOLOGY

The obstruction to LV outflow produces a systolic pressure gradient between the LV and aorta. When severe obstruction is suddenly produced experimentally, the LV responds by dilation and reduction of stroke volume. However, in some patients, the obstruction may be present at birth and/or increase gradually over the course of many years, and LV contractile performance is maintained by the presence of concentric LV hypertrophy. Initially, this serves as an adaptive mechanism because it reduces toward normal the systolic stress developed by the myocardium, as predicted by the Laplace relation ($S = Pr/h$, where S = systolic wall stress, P = pressure, r = radius, and h = wall thickness). A large transaortic valve pressure gradient may exist for many years without a reduction in cardiac output (CO) or LV dilation; ultimately, however, excessive hypertrophy becomes maladaptive, LV systolic function declines because of afterload mismatch, abnormalities of diastolic function progress, and irreversible myocardial fibrosis develops.

A mean systolic pressure gradient >40 mmHg with a normal CO or an effective aortic orifice area of approximately <1 cm² (or approximately <0.6 cm²/m² body surface area in a normal-sized adult)—i.e., less than approximately one-third of the normal orifice area—is generally considered to represent severe obstruction to LV outflow. The elevated LV end-diastolic pressure observed in many patients with severe AS and preserved ejection fraction (EF) signifies the presence of diminished compliance of the hypertrophied LV. Although the CO at rest is within normal limits in most patients with severe AS, it usually fails to rise normally during exercise. Loss of an appropriately timed, vigorous atrial contraction, as occurs in atrial fibrillation (AF) or atrioventricular dissociation, may cause rapid progression of symptoms. Late in the course, contractile function deteriorates because of afterload excess, the CO and LV–aortic pressure gradient decline, and the mean left atrial (LA), pulmonary artery (PA), and right ventricular (RV) pressures rise. LV performance can be further compromised by superimposed coronary artery disease (CAD). Stroke volume (and thus CO) can also be reduced in

patients with significant hypertrophy and a small LV cavity despite a normal EF. Low-flow, low-gradient AS (with either reduced or normal LV systolic function) is both a diagnostic and therapeutic challenge.

The hypertrophied LV causes an increase in myocardial oxygen requirements. In addition, even in the absence of obstructive CAD, coronary blood flow is impaired to the extent that ischemia can be precipitated under conditions of excess demand. Capillary density is reduced relative to wall thickness, compressive forces are increased, and the elevated LV end-diastolic pressure reduces the coronary driving pressure. The subendocardium is especially vulnerable to ischemia by this mechanism.

SYMPTOMS

AS is rarely of clinical importance until the valve orifice has narrowed to approximately 1 cm². Even severe AS may exist for many years without producing any symptoms because of the ability of the hypertrophied LV to generate the elevated intraventricular pressures required to maintain a normal stroke volume. Once symptoms occur, valve replacement is indicated.

Most patients with pure or predominant AS have gradually increasing obstruction over years but do not become symptomatic until the sixth to eighth decades. Adult patients with BAV disease, however, develop significant valve dysfunction and symptoms one to two decades sooner. Exertional dyspnea, angina pectoris, and syncope are the three cardinal symptoms. Often, there is a history of insidious progression of fatigue and dyspnea associated with gradual curtailment of activities and reduced effort tolerance. Dyspnea results primarily from elevation of the pulmonary capillary pressure caused by elevations of LV diastolic pressures secondary to impaired relaxation and reduced LV compliance. Angina pectoris usually develops somewhat later and reflects an imbalance between the augmented myocardial oxygen requirements and reduced oxygen availability. CAD may or may not be present, although its coexistence is common among AS patients older than age 65. Exertional syncope may result from a decline in arterial pressure caused by vasodilation in the exercising muscles and inadequate vasoconstriction in nonexercising muscles in the face of a fixed CO, or from a sudden fall in CO produced by an arrhythmia.

Because the CO at rest is usually well maintained until late in the course, marked fatigability, weakness, peripheral cyanosis, cachexia, and other clinical manifestations of a low CO are usually not prominent until this stage is reached. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, i.e., symptoms of LV failure, also occur only in the advanced stages of the disease. Severe pulmonary hypertension leading to RV

failure and systemic venous hypertension, hepatomegaly, AF, and tricuspid regurgitation (TR) are usually late findings in patients with isolated severe AS.

When AS and mitral stenosis (MS) coexist, the reduction in flow (CO) induced by MS lowers the pressure gradient across the aortic valve and, thereby, masks many of the clinical findings produced by AS. The transaortic pressure gradient can be increased in patients with concomitant aortic regurgitation (AR) due to higher aortic valve flow rates.

PHYSICAL FINDINGS

The rhythm is generally regular until late in the course; at other times, AF should suggest the possibility of associated mitral valve disease. The systemic arterial pressure is usually within normal limits. In the late stages, however, when stroke volume declines, the systolic pressure may fall and the pulse pressure narrow. The carotid arterial pulse rises slowly to a delayed peak (pulsus parvus et tardus). A thrill or anacrotic “shudder” may be palpable over the carotid arteries, more commonly the left. In the elderly, the stiffening of the arterial wall may mask this important physical sign. In many patients, the a wave in the jugular venous pulse is accentuated. This results from the diminished distensibility of the RV cavity caused by the bulging, hypertrophied interventricular septum.

The LV impulse is sometimes displaced laterally in the later stages of the disease. A double apical impulse (with a palpable S₄) may be recognized, particularly with the patient in the left lateral recumbent position. A systolic thrill may be present at the base of the heart to the right of the sternum when leaning forward or in the suprasternal notch.

Auscultation

An early systolic ejection sound is frequently audible in children, adolescents, and young adults with congenital BAV disease. This sound usually disappears when the valve becomes calcified and rigid. As AS increases in severity, LV systole may become prolonged so that the aortic valve closure sound no longer precedes the pulmonic valve closure sound, and the two components may become synchronous, or aortic valve closure may even follow pulmonic valve closure, causing paradoxical splitting of S₂ (**Chap. 9**). The sound of aortic valve closure can be heard most frequently in patients with AS who have pliable valves, and calcification diminishes the intensity of this sound. Frequently, an S₄ is audible at the apex and reflects the presence of LV hypertrophy and an elevated LV end-diastolic pressure; an S₃ generally occurs late in the course, when the LV dilates and its systolic function becomes severely compromised.

The murmur of AS is characteristically an ejection (mid) systolic murmur that commences shortly after the S_1 , increases in intensity to reach a peak toward the middle of ejection, and ends just before aortic valve closure. It is characteristically low-pitched, rough and rasping in character, and loudest at the base of the heart, most commonly in the second right intercostal space. It is transmitted upward along the carotid arteries. Occasionally it is transmitted downward and to the apex, where it may be confused with the systolic murmur of mitral regurgitation (MR) (Gallavardin effect). In almost all patients with severe obstruction and preserved CO, the murmur is at least grade III/VI. In patients with mild degrees of obstruction or in those with severe stenosis with heart failure and low CO in whom the stroke volume and, therefore, the transvalvular flow rate are reduced, the murmur may be relatively soft and brief.

LABORATORY EXAMINATION

ECG

In most patients with severe AS, there is LV hypertrophy. In advanced cases, ST-segment depression and T-wave inversion (LV “strain”) in standard leads I and aVL and in the left precordial leads are evident. However, there is no close correlation between the ECG and the hemodynamic severity of obstruction, and the absence of ECG signs of LV hypertrophy does not exclude severe obstruction. Many patients with AS have systemic hypertension, which can also contribute to the development of hypertrophy.

Echocardiogram

The key findings on TTE are thickening, calcification, and reduced systolic opening of the valve leaflets and LV hypertrophy. Eccentric closure of the aortic valve cusps is characteristic of congenitally bicuspid valves. TEE imaging can display the obstructed orifice extremely well, but it is not routinely required for accurate characterization of AS. The valve gradient and aortic valve area can be estimated by Doppler measurement of the transaortic velocity. Severe AS is defined by a valve area $<1 \text{ cm}^2$, whereas moderate AS is defined by a valve area of $1\text{--}1.5 \text{ cm}^2$ and mild AS by a valve area of $1.5\text{--}2 \text{ cm}^2$. Aortic valve sclerosis, conversely, is accompanied by a jet velocity of less than 2.5 meters/s (peak gradient $<25 \text{ mmHg}$). LV dilation and reduced systolic shortening reflect impairment of LV function. There is increasing experience with the use of longitudinal strain and strain rate to characterize earlier changes in LV systolic function, well before a decline in EF can be appreciated. Doppler indices of impaired diastolic function are frequently seen.

Echocardiography is useful for identifying coexisting valvular abnormalities; for differentiating valvular AS from other forms of LV outflow obstruction; and for measurement of the aortic root and proximal ascending aortic dimensions. These aortic measurements are particularly important for patients with BAV disease. Dobutamine stress echocardiography is useful for the evaluation of patients with AS and severe LV systolic dysfunction (low-flow, low-gradient, severe AS with reduced EF), in whom the severity of the AS can often be difficult to judge. Patients with severe AS (i.e., valve area $<1 \text{ cm}^2$) with a relatively low mean gradient ($<40 \text{ mmHg}$) despite a normal EF (low-flow, low-gradient, severe AS with normal EF) are often hypertensive, and efforts to control their systemic blood pressure should be optimized before Doppler echocardiography is repeated. The use of dobutamine stress echocardiography in this setting is under investigation. When there is continued uncertainty regarding the severity of AS in patients with reduced CO, quantitative analysis of the amount of aortic valve calcium with chest computed tomography (CT) may be helpful.

Chest x-ray

The chest x-ray may show no or little overall cardiac enlargement for many years. Hypertrophy without dilation may produce some rounding of the cardiac apex in the frontal projection and slight backward displacement in the lateral view. A dilated proximal ascending aorta may be seen along the upper right heart border in the frontal view. Aortic valve calcification may be discernible in the lateral view, but is usually readily apparent on fluoroscopic examination or by echocardiography; the absence of valvular calcification on fluoroscopy in an adult suggests that severe valvular AS is not present. In later stages of the disease, as the LV dilates, there is increasing roentgenographic evidence of LV enlargement, pulmonary congestion, and enlargement of the LA, PA, and right heart chambers.

Catheterization

Right and left heart catheterization for invasive assessment of AS is performed infrequently but can be useful when there is a discrepancy between the clinical and noninvasive findings. Concern has been raised that attempts to cross the aortic valve for measurement of LV pressures are associated with a risk of cerebral embolization. Catheterization is also useful in three distinct categories of patients: (1) patients with multivalvular disease, in whom the role played by each valvular deformity should be defined to aid in the planning of operative treatment; (2) young, asymptomatic patients

264 with noncalcific congenital AS, to define the severity of obstruction to LV outflow, because operation or percutaneous aortic balloon valvuloplasty (PABV) may be indicated in these patients if severe AS is present, even in the absence of symptoms; and (3) patients in whom it is suspected that the obstruction to LV outflow may not be at the level of the aortic valve but rather at the sub- or supra- valvular level.

Coronary angiography is indicated to screen for CAD in appropriate patients with severe AS who are being considered for surgery. The incidence of significant CAD for which bypass grafting is indicated at the time of aortic valve replacement (AVR) exceeds 50% among adult patients.

NATURAL HISTORY

Death in patients with severe AS occurs most commonly in the seventh and eighth decades. Based on data obtained at postmortem examination in patients before surgical treatment became widely available, the average time to death after the onset of various symptoms was as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; congestive heart failure, 1.5–2 years. Moreover, in >80% of patients who died with AS, symptoms had existed for <4 years. Among adults dying with valvular AS, sudden death, which presumably resulted from an arrhythmia, occurred in 10–20%; however, most sudden deaths occurred in patients who had previously been symptomatic. Sudden death as the first manifestation of severe AS is very uncommon (<1% per year) in asymptomatic adult patients. Calcific AS is a progressive disease, with an annual reduction in valve area averaging 0.1 cm² and annual increases in the peak jet velocity and mean valve gradient averaging 0.3 meters/s and 7 mmHg, respectively (Table 23-2).

TABLE 23-2

MORTALITY RATES AFTER AORTIC VALVE SURGERY ^a		
OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
AVR (isolated)	14,795	2.3
AVR + CAB	9158	4.2
AVR + MVR	876	8.8

^aData are for the first two quarters of calendar year 2013, during which 1004 sites reported a total of 135,666 procedures. Data are available from the Society of Thoracic Surgeons at http://www.sts.org/sites/default/files/documents/2013_3rdHarvestExecutiveSummary.pdf. Abbreviations: AVR, aortic valve replacement; CAB, coronary artery bypass; MVR, mitral valve replacement.

TREATMENT Aortic Stenosis

MEDICAL TREATMENT In patients with severe AS (valve area <1 cm²), strenuous physical activity and competitive sports should be avoided, even in the asymptomatic stage (Fig. 23-2). Care must be taken to avoid dehydration and hypovolemia to protect against a significant reduction in CO. Medications used for the treatment of hypertension or CAD, including beta blockers and angiotensin-converting enzyme (ACE) inhibitors, are generally safe for asymptomatic patients with preserved LV systolic function. Nitroglycerin is helpful in relieving angina pectoris in patients with CAD. Retrospective studies have shown that patients with degenerative calcific AS who receive HMG-CoA reductase inhibitors (“statins”) exhibit slower progression of leaflet calcification and aortic valve area reduction than those who do not. However, randomized prospective studies with either high-dose atorvastatin or combination simvastatin/ezetimibe have failed to show a measurable effect on valve-related outcomes. The use of statin medications should continue to be driven by considerations regarding primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events. ACE inhibitors have not been studied prospectively for AS-related outcomes. The need for endocarditis prophylaxis is restricted to AS patients with a prior history of endocarditis.

SURGICAL TREATMENT Asymptomatic patients with calcific AS and severe obstruction should be followed carefully for the development of symptoms and by serial echocardiograms for evidence of deteriorating LV function. Operation is indicated in patients with severe AS (valve area <1 cm² or 0.6 cm²/m² body surface area) who are symptomatic, those who exhibit LV systolic dysfunction (EF <50%), and those with BAV disease and an aneurysmal root or ascending aorta (maximal dimension >5.5 cm). Operation for aneurysm disease is recommended at smaller aortic diameters (4.5–5.0 cm) for patients with a family history of an aortic catastrophe and for patients who exhibit rapid aneurysm growth (>0.5 cm/year). Patients with asymptomatic moderate or severe AS who are referred for coronary artery bypass grafting surgery should also have AVR. In patients without heart failure, the operative risk of AVR (including patients with AS or AR) is approximately 2% (Table 23-2) but increases as a function of age and the need for concomitant aortic surgery or coronary revascularization with bypass grafting. The indications for AVR in the asymptomatic patient have been the subject of intense debate over the past 5 years, as surgical outcomes in selected patients have continued to improve. Relative indications for which surgery can be considered include an abnormal response to treadmill exercise; rapid progression of AS, especially when urgent access to medical care might be compromised; very severe AS, defined by an aortic valve jet velocity >5 meters/s or mean gradient >60 mmHg and low operative risk; and excessive LV hypertrophy in the absence of systemic

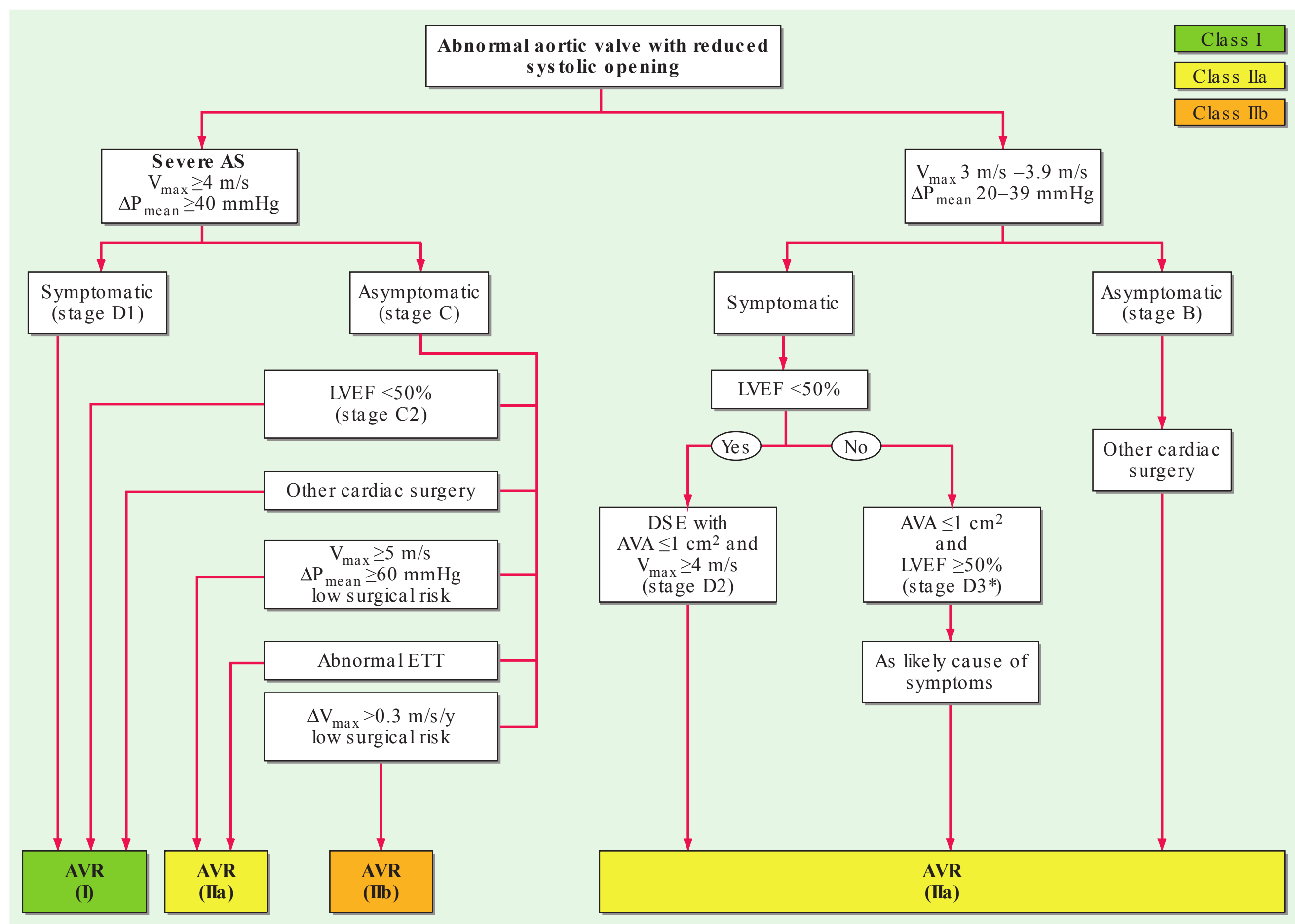


FIGURE 23-2

Management strategy for patients with aortic stenosis. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. The class designations refer to the American College of Cardiology/American Heart Association methodology for treatment recommendations. Class I recommendations should be performed or are indicated; Class IIa recommendations are considered reasonable to perform; Class IIb recommendations may be considered. The stages refer to the stages of progression of the disease. At disease stage A, risk factors are present for the development of valve dysfunction; stage B refers to progressive, mild-moderate, asymptomatic valve disease; stage C disease is severe in nature but clinically asymptomatic; stage C1 characterizes asymptomatic patients with severe valve disease

hypertension. Exercise testing can be safely performed in the asymptomatic patient, as many as one-third of whom will show signs of functional impairment.

Operation should be carried out promptly after symptom onset. In patients with low-flow, low-gradient severe AS with reduced LVEF, the perioperative mortality risk is high (15–20%), and evidence of myocardial disease may persist even

but compensated ventricular function; stage C2 refers to asymptomatic, severe disease with ventricular decompensation; stage D refers to severe, symptomatic valve disease. With aortic stenosis, stage D1 refers to symptomatic patients with severe aortic stenosis and a high valve gradient (>40 mmHg mean gradient); stage D2 comprises patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and low left ventricular ejection fraction; and stage D3 characterizes patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and preserved left ventricular ejection fraction (paradoxical, low-flow, low-gradient severe aortic stenosis). AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean} , mean pressure gradient; and V_{max} , maximum velocity. (Adapted from RANishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

when the operation is technically successful. Long-term post-operative survival correlates with preoperative LV function. Nonetheless, in view of the even worse prognosis of such patients when they are treated medically, there is usually little choice but to advise valve replacement, especially in patients in whom contractile reserve can be demonstrated by dobutamine stress echocardiography (defined by a $\geq 20\%$ increase

in stroke volume after dobutamine challenge). Patients in this high surgical risk group may benefit from transcatheter aortic valve replacement (TAVR, see below). The treatment of patients with low-flow, low-gradient severe AS with normal LVEF is also difficult. Outcomes appear to be better with surgery compared with conservative medical care for symptomatic patients with this type of “paradoxical” low-flow AS, but more research is needed to guide therapeutic decision-making. In patients in whom severe AS and CAD coexist, relief of the AS and revascularization may sometimes result in striking clinical and hemodynamic improvement (Table 23-2).

Because many patients with calcific AS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary function before AVR is recommended. Age alone is not a contraindication to AVR for AS. The perioperative mortality rate depends to a substantial extent on the patient's preoperative clinical and hemodynamic state. Treatment decisions for AS patients who are not at low operative risk should be made by a multidisciplinary heart team with representation from general cardiology, interventional cardiology, imaging, cardiac surgery, and other allied specialties as needed, including geriatrics. The 10-year survival rate of older adult patients with AVR is approximately 60%. Approximately 30% of bioprosthetic valves evidence primary valve failure in 10 years, requiring re-replacement, and an approximately equal percentage of patients with mechanical prostheses develop significant hemorrhagic complications as a consequence of

treatment with vitamin K antagonists. Homograft AVR is usually reserved for patients with aortic valve endocarditis.

The Ross procedure involves replacement of the diseased aortic valve with the autologous pulmonic valve and implantation of a homograft in the native pulmonic position. Its use has declined considerably in the United States because of the technical complexity of the procedure and the incidence of late postoperative aortic root dilation and autograft failure with AR. There is also a low incidence of pulmonary homograft stenosis.

PERCUTANEOUS AORTIC BALLOON VALVULOPLASTY (PABV) This procedure is preferable to operation in many children and young adults with congenital, noncalcific AS (**Chap. 22**). It is not commonly used as definitive therapy in adults with severe calcific AS because of a very high restenosis rate (80% within 1 year) and the risk of procedural complications, but on occasion, it has been used successfully as a “bridge to operation” in patients with severe LV dysfunction and shock who are too ill to tolerate surgery. It is performed routinely as part of the TAVR procedure (see below).

TRANSCATHETER AORTIC VALVE REPLACEMENT TAVR for treatment of AS has been performed in more than 50,000 prohibitive- or high-surgical-risk adult patients worldwide using one of two available systems, a balloon-expandable valve and a self-expanding valve, both of which incorporate a pericardial prosthesis (**Fig. 23-3**). More than 250 U.S. centers now offer this procedure. TAVR is most frequently



FIGURE 23-3

Balloon-expandable (A) and self-expanding (B) valves for transcatheter aortic valve replacement (TAVR). B, inflated balloon; N, nose cone; V, valve. (Part A, courtesy of Edwards Lifesciences, Irvine, CA; with permission. NovaFlex+ is a trademark of Edwards

Lifesciences Corporation. Part B, © Medtronic, Inc. 2015. Medtronic CoreValve Transcatheter Aortic Valve. CoreValve is a registered trademark of Medtronic, Inc.)

performed via the transfemoral route, although trans-LV apical, subclavian, carotid, and ascending aortic routes have been used. Aortic balloon valvuloplasty under rapid RV pacing is performed as a first step to create an orifice of sufficient size for the prosthesis. Procedural success rates exceed 90%. Among elderly patients with severe AS who are considered inoperable (i.e., prohibitive surgical risk), 1- and 2-year survival rates are significantly higher with TAVR compared with medical therapy (including PABV) (**Fig. 23-4**). One- and 2-year survival rates are essentially equal for high-surgical-risk patients treated with TAVR or surgical AVR (SAVR) (**Fig. 23-5**). TAVR is associated

with an early hazard for stroke and a higher incidence of postprocedural, paravalvular AR, a risk factor for mortality over the next 2 years. Postprocedural heart block requiring permanent pacemaker therapy is observed significantly more frequently with the self-expanding valve. Valve performance characteristics are excellent. Overall outcomes with this transformative technology have been very favorable and have allowed the extension of AVR to groups of patients previously considered at high or prohibitive risk for conventional surgery. Nevertheless, some patients are not candidates for this procedure because their comorbidity profile, including an assessment of frailty, would make its undertaking inappropriate. The heart team is specifically charged with making challenging decisions of this nature. The use of these devices for the treatment of patients at intermediate operative risk and for those with structural deterioration of bioprosthetic aortic and mitral valves (“valve-in-valve”), as an alternative to reoperative valve replacement, is under active study.

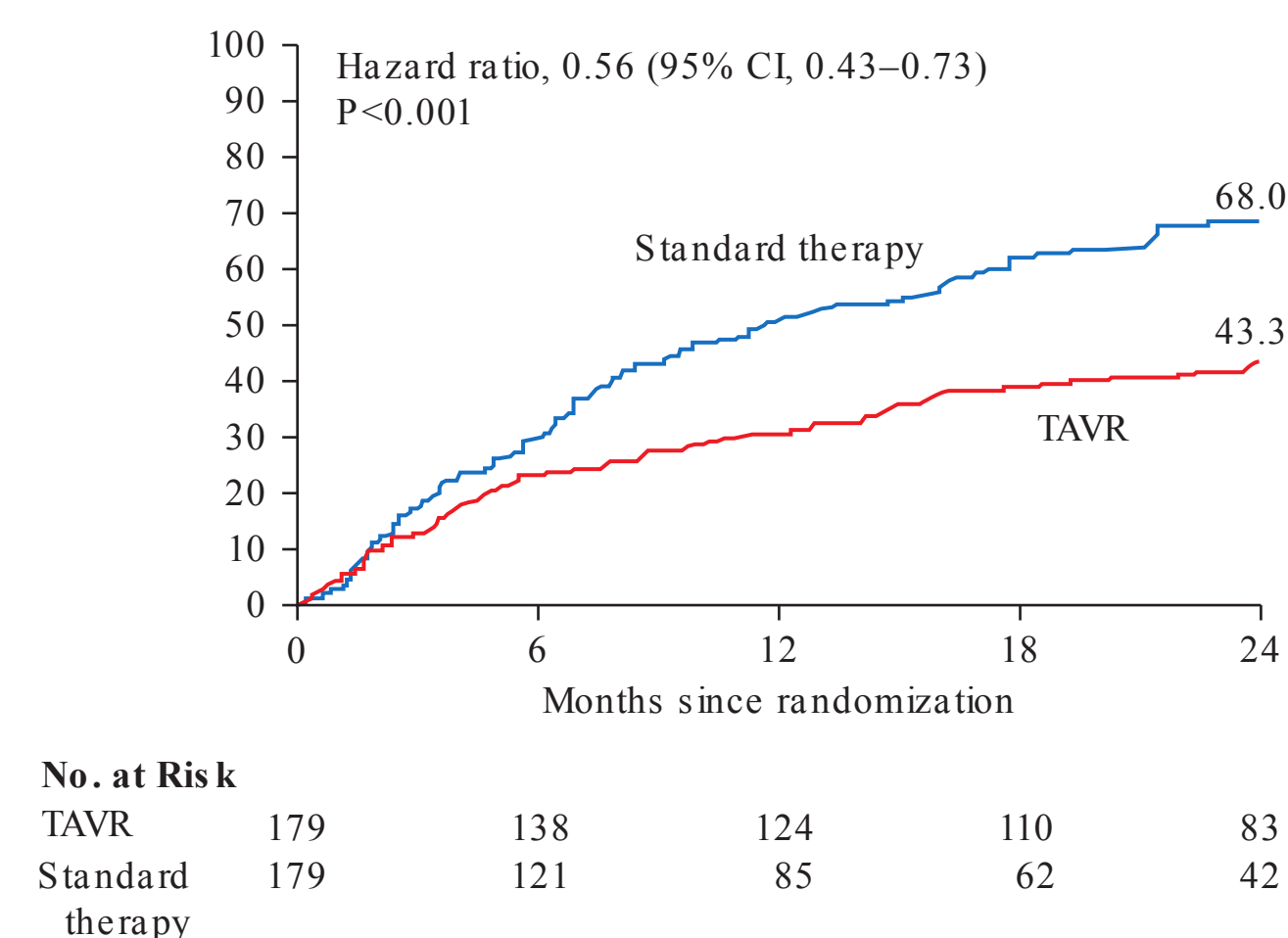


FIGURE 23-4

Twenty-four-month outcomes following transcatheter aortic valve replacement (TAVR) for inoperable patients in the PARTNER I trial (cohort B). CI, confidence interval. (Adapted from RR Makkar et al: *N Engl J Med* 366:1696, 2012; with permission.)

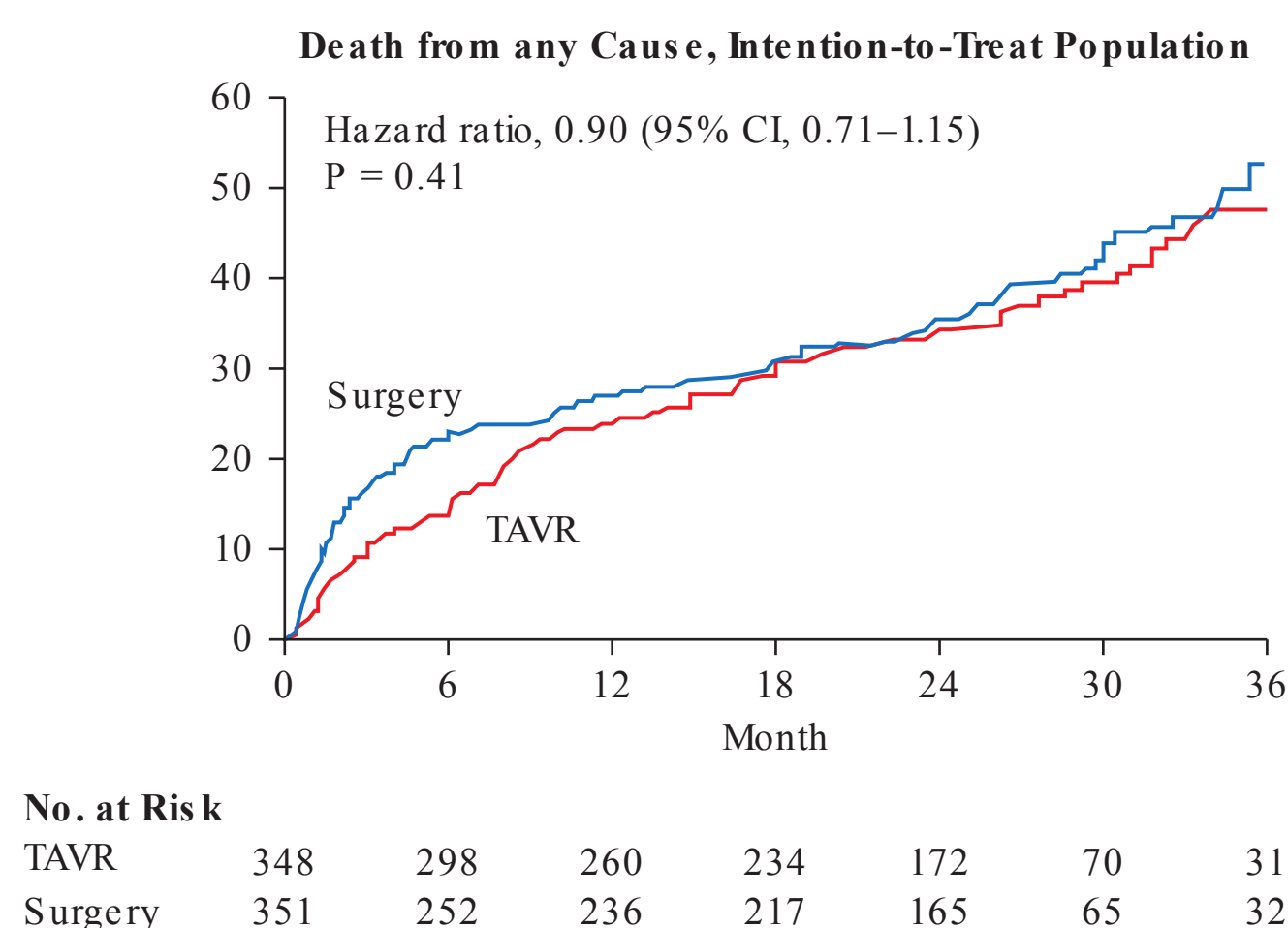


FIGURE 23-5

Thirty-six-month outcomes following transcatheter aortic valve replacement (TAVR) for high-surgical-risk patients (cohort A) in the PARTNER I trial. CI, confidence interval. (Adapted from SK Kodali et al: *New Engl J Med* 366:1686, 2012.)

AORTIC REGURGITATION

ETIOLOGY

(Table 23-1) AR may be caused by primary valve disease or by primary aortic root disease.

Primary valve disease

Rheumatic disease results in thickening, deformity, and shortening of the individual aortic valve cusps, changes that prevent their proper opening during systole and closure during diastole. A rheumatic origin is much less common in patients with isolated AR who do not have associated rheumatic mitral valve disease. Patients with congenital BAV disease may develop predominant AR, and approximately 20% of patients will require aortic valve surgery between 10 and 40 years of age. Congenital fenestrations of the aortic valve occasionally produce mild AR. Membranous subaortic stenosis often leads to thickening and scarring of the aortic valve leaflets with secondary AR. Prolapse of an aortic cusp, resulting in progressive chronic AR, occurs in approximately 15% of patients with ventricular septal defect (**Chap. 22**) but may also occur as an isolated phenomenon or as a consequence of myxomatous degeneration sometimes associated with mitral and/or tricuspid valve involvement.

AR may result from infective endocarditis, which can develop on a valve previously affected by rheumatic disease, a congenitally deformed valve, or on a normal aortic valve, and may lead to perforation or erosion of one or more leaflets. The aortic valve leaflets may become scarred and retracted during the course of syphilis or ankylosing spondylitis and contribute further to the AR

that derives primarily from the associated root disease. Although traumatic rupture or avulsion of an aortic cusp is an uncommon cause of acute AR, it represents the most frequent serious lesion in patients surviving nonpenetrating cardiac injuries. The coexistence of hemodynamically significant AS with AR usually excludes all the rarer forms of AR because it occurs almost exclusively in patients with rheumatic or congenital AR. In patients with AR due to primary valvular disease, dilation of the aortic annulus may occur secondarily and lead to worsening regurgitation.

Primary aortic root disease

AR also may be due entirely to marked aortic annular dilation, i.e., aortic root disease, without primary involvement of the valve leaflets; widening of the aortic annulus and separation of the aortic leaflets are responsible for the AR (**Chap. 46**). Medial degeneration of the ascending aorta, which may or may not be associated with other manifestations of Marfan's syndrome; idiopathic dilation of the aorta; annuloaortic ectasia; osteogenesis imperfecta; and severe, chronic hypertension may all widen the aortic annulus and lead to progressive AR. Occasionally AR is caused by retrograde dissection of the aorta involving the aortic annulus. Syphilis and ankylosing spondylitis, both of which may affect the aortic leaflets, may also be associated with cellular infiltration and scarring of the media of the thoracic aorta, leading to aortic dilation, aneurysm formation, and severe regurgitation. In syphilis of the aorta, now a very rare condition, the involvement of the intima may narrow the coronary ostia, which in turn may be responsible for myocardial ischemia.

PATHOPHYSIOLOGY

The total stroke volume ejected by the LV (i.e., the sum of the effective forward stroke volume and the volume of blood that regurgitates back into the LV) is increased in patients with AR. In patients with severe AR, the volume of regurgitant flow may equal the effective forward stroke volume. In contrast to MR, in which a portion of the LV stroke volume is delivered into the low-pressure LA, in AR the entire LV stroke volume is ejected into a high-pressure zone, the aorta. An increase in the LV end-diastolic volume (increased preload) constitutes the major hemodynamic compensation for AR. The dilation and eccentric hypertrophy of the LV allow this chamber to eject a larger stroke volume without requiring any increase in the relative shortening of each myofibril. Therefore, severe AR may occur with a normal effective forward stroke volume and a normal LVEF (total [forward plus regurgitant] stroke volume/end-diastolic volume), together with an elevated LV

end-diastolic pressure and volume. However, through the operation of Laplace's law, LV dilation increases the LV systolic tension required to develop any given level of systolic pressure. Chronic AR is, thus, a state in which LV preload and afterload are both increased. Ultimately, these adaptive measures fail. As LV function deteriorates, the end-diastolic volume rises further and the forward stroke volume and EF decline. Deterioration of LV function often precedes the development of symptoms. Considerable thickening of the LV wall also occurs with chronic AR, and at autopsy, the hearts of these patients may be among the largest encountered, sometimes weighing >1000 g.

The reverse pressure gradient from aorta to LV, which drives the AR flow, falls progressively during diastole, accounting for the decrescendo nature of the diastolic murmur. Equilibration between aortic and LV pressures may occur toward the end of diastole in patients with chronic severe AR, particularly when the heart rate is slow. In patients with acute severe AR, the LV is unprepared for the regurgitant volume load. LV compliance is normal or reduced, and LV diastolic pressures rise rapidly, occasionally to levels >40 mmHg. The LV pressure may exceed the LA pressure toward the end of diastole, and this reversed pressure gradient closes the mitral valve prematurely.

In patients with chronic severe AR, the effective forward CO usually is normal or only slightly reduced at rest, but often it fails to rise normally during exertion. An early sign of LV dysfunction is a reduction in the EF. In advanced stages, there may be considerable elevation of the LA, PA wedge, PA, and RV pressures and lowering of the forward CO at rest.

Myocardial ischemia may occur in patients with AR because myocardial oxygen requirements are elevated by LV dilation, hypertrophy, and elevated LV systolic tension, and coronary blood flow may be compromised. A large fraction of coronary blood flow occurs during diastole, when arterial pressure is low, thereby reducing coronary perfusion or driving pressure. This combination of increased oxygen demand and reduced supply may cause myocardial ischemia, particularly of the sub-endocardium, even in the absence of epicardial CAD.

HISTORY

Approximately three-fourths of patients with pure or predominant valvular AR are men; women predominate among patients with primary valvular AR who have associated rheumatic mitral valve disease. A history compatible with infective endocarditis may sometimes be elicited from patients with rheumatic or congenital involvement of the aortic valve, and the infection often precipitates or seriously aggravates pre-existing symptoms.

In patients with acute severe AR, as may occur in infective endocarditis, aortic dissection, or trauma, the LV cannot dilate sufficiently to maintain stroke volume, and LV diastolic pressure rises rapidly with associated marked elevations of LA and PA wedge pressures. Pulmonary edema and/or cardiogenic shock may develop rapidly.

Chronic severe AR may have a long latent period, and patients may remain relatively asymptomatic for as long as 10–15 years. However, uncomfortable awareness of the heartbeat, especially on lying down, may be an early complaint. Sinus tachycardia, during exertion or with emotion, or premature ventricular contractions may produce particularly uncomfortable palpitations as well as head pounding. These complaints may persist for many years before the development of exertional dyspnea, usually the first symptom of diminished cardiac reserve. The dyspnea is followed by orthopnea, paroxysmal nocturnal dyspnea, and excessive diaphoresis. Anginal chest pain even in the absence of CAD may occur in patients with severe AR, even in younger patients. Anginal pain may develop at rest as well as during exertion. Nocturnal angina may be a particularly troublesome symptom, and it may be accompanied by marked diaphoresis. The anginal episodes can be prolonged and often do not respond satisfactorily to sublingual nitroglycerin. Systemic fluid accumulation, including congestive hepatomegaly and ankle edema, may develop late in the course of the disease.

PHYSICAL FINDINGS

In chronic severe AR, the jarring of the entire body and the bobbing motion of the head with each systole can be appreciated, and the abrupt distention and collapse of the larger arteries are easily visible. The examination should be directed toward the detection of conditions predisposing to AR, such as bicuspid valve, endocarditis, Marfan's syndrome, and ankylosing spondylitis.

Arterial pulse

A rapidly rising “water-hammer” pulse, which collapses suddenly as arterial pressure falls rapidly during late systole and diastole (Corrigan's pulse), and capillary pulsations, an alternate flushing and paling of the skin at the root of the nail while pressure is applied to the tip of the nail (Quincke's pulse), are characteristic of chronic severe AR. A booming “pistol-shot” sound can be heard over the femoral arteries (Traube's sign), and a to-and-fro murmur (Duroziez's sign) is audible if the femoral artery is lightly compressed with a stethoscope.

The arterial pulse pressure is widened as a result of both systolic hypertension and a lowering of the diastolic pressure. The measurement of arterial diastolic pressure with a sphygmomanometer may be complicated by the

fact that systolic sounds are frequently heard with the cuff completely deflated. However, the level of cuff pressure at the time of muffling of the Korotkoff sounds (phase IV) generally corresponds fairly closely to the true intraarterial diastolic pressure. As the disease progresses and the LV end-diastolic pressure rises, the arterial diastolic pressure may actually rise as well, because the aortic diastolic pressure cannot fall below the LV end-diastolic pressure. For the same reason, acute severe AR may also be accompanied by only a slight widening of the pulse pressure. Such patients are invariably tachycardic as the heart rate increases in an attempt to preserve the CO.

Palpation

In patients with chronic severe AR, the LV impulse is heaving and displaced laterally and inferiorly. The systolic expansion and diastolic retraction of the apex are prominent. A diastolic thrill may be palpable along the left sternal border in thin-chested individuals, and a prominent systolic thrill may be palpable in the suprasternal notch and transmitted upward along the carotid arteries. This systolic thrill and the accompanying murmur do not necessarily signify the coexistence of AS. In some patients with AR or with combined AS and AR, the carotid arterial pulse may be bisferiens, i.e., with two systolic waves separated by a trough (see Fig. 9-2D).

Auscultation

In patients with severe AR, the aortic valve closure sound (A_2) is usually absent. A systolic ejection sound is audible in patients with BAV disease, and occasionally an S_4 also may be heard. The murmur of chronic AR is typically a high-pitched, blowing, decrescendo diastolic murmur, heard best in the third intercostal space along the left sternal border (see Fig. 9-5B). In patients with mild AR, this murmur is brief, but as the severity increases, it generally becomes louder and longer, indeed holodiastolic. When the murmur is soft, it can be heard best with the diaphragm of the stethoscope and with the patient sitting up, leaning forward, and with the breath held in forced expiration. In patients in whom the AR is caused by primary valvular disease, the diastolic murmur is usually louder along the left than the right sternal border. However, when the murmur is heard best along the right sternal border, it suggests that the AR is caused by aneurysmal dilation of the aortic root. “Cooing” or musical diastolic murmurs suggest eversion of an aortic cusp vibrating in the regurgitant stream.

A mid-systolic ejection murmur is frequently audible in isolated AR. It is generally heard best at the base of the heart and is transmitted along the carotid arteries. This murmur may be quite loud without signifying aortic obstruction. A third murmur sometimes heard in

patients with severe AR is the Austin Flint murmur, a soft, low-pitched, rumbling mid-to-late diastolic murmur. It is probably produced by the diastolic displacement of the anterior leaflet of the mitral valve by the AR stream and is not associated with hemodynamically significant mitral obstruction. The auscultatory features of AR are intensified by strenuous and sustained handgrip, which augments systemic vascular resistance.

In acute severe AR, the elevation of LV end-diastolic pressure may lead to early closure of the mitral valve, a soft S_1 , a pulse pressure that is not particularly wide, and a soft, short, early diastolic murmur of AR.

LABORATORY EXAMINATION

ECG

In patients with chronic severe AR, the ECG signs of LV hypertrophy become manifest (**Chap. 11**). In addition, these patients frequently exhibit ST-segment depression and T-wave inversion in leads I, aVL, V_5 , and V_6 ("LV strain"). Left-axis deviation and/or QRS prolongation denote diffuse myocardial disease, generally associated with patchy fibrosis, and usually signify a poor prognosis.

Echocardiogram

LV size is increased in chronic AR and systolic function is normal or even supernormal until myocardial contractility declines, as signaled by a decrease in EF or increase in the end-systolic dimension. A rapid, high-frequency diastolic fluttering of the anterior mitral leaflet produced by the impact of the regurgitant jet is a characteristic finding. The echocardiogram is also useful in determining the cause of AR, by detecting dilation of the aortic annulus and root, aortic dissection (**see Fig. 12-5**), or primary leaflet pathology. With severe AR, the central jet width assessed by color flow Doppler imaging exceeds 65% of the LV outflow tract, the regurgitant volume is ≥ 60 mL/beat, the regurgitant fraction is $\geq 50\%$, and there is diastolic flow reversal in the proximal descending thoracic aorta. The continuous-wave Doppler profile of the AR jet shows a rapid deceleration time in patients with acute severe AR, due to the rapid increase in LV diastolic pressure. Surveillance transthoracic echocardiography forms the cornerstone of longitudinal follow-up and allows for the early detection of changes in LV size and/or function. For patients in whom transthoracic echocardiography (TTE) is limited by poor acoustical windows or inadequate semiquantitative assessment of LV function or the severity of the regurgitation, cardiac magnetic resonance imaging (MRI) can be performed. This modality also allows for accurate assessment of aortic size and contour. Transesophageal echocardiography (TEE) can also provide detailed anatomic assessment of the valve, root, and portions of the aorta.

Chest x-ray

In chronic severe AR, the apex is displaced downward and to the left in the frontal projection. In the left anterior oblique and lateral projections, the LV is displaced posteriorly and encroaches on the spine. When AR is caused by primary disease of the aortic root, aneurysmal dilation of the aorta may be noted, and the aorta may fill the retrosternal space in the lateral view. Echocardiography, cardiac MRI, and chest CT angiography are more sensitive than the chest x-ray for the detection of root and ascending aortic enlargement.

Cardiac catheterization and angiography

When needed, right and left heart catheterization with contrast aortography can provide confirmation of the magnitude of regurgitation and the status of LV function. Coronary angiography is performed routinely in appropriate patients prior to surgery.

TREATMENT Aortic Regurgitation

ACUTE AORTIC REGURGITATION Patients with acute severe AR may respond to intravenous diuretics and vasodilators (such as sodium nitroprusside), but stabilization is usually short-lived and operation is indicated urgently (**Fig. 23-6**). Intraaortic balloon counterpulsation is contraindicated. Beta blockers are also best avoided so as not to reduce the CO further or slow the heart rate, thus allowing more time for diastolic filling of the LV. Surgery is the treatment of choice and is usually necessary within 24 h of diagnosis.

CHRONIC AORTIC REGURGITATION Early symptoms of dyspnea and effort intolerance respond to treatment with diuretics; vasodilators (ACE inhibitors, dihydropyridine calcium channel blockers, or hydralazine) may be useful as well. Surgery can then be performed in a more controlled setting. The use of vasodilators to extend the compensated phase of chronic severe AR before the onset of symptoms or the development of LV dysfunction is more controversial and less well established. Systolic blood pressure should be controlled (goal <140 mmHg) in patients with chronic AR, and vasodilators are an excellent first choice as antihypertensive agents. It is often difficult to achieve adequate control because of the increased stroke volume that accompanies severe AR. Cardiac arrhythmias and systemic infections are poorly tolerated in patients with severe AR and must be treated promptly and vigorously. Although nitroglycerin and long-acting nitrates are not as helpful in relieving anginal pain as they are in patients with ischemic heart disease, they are worth a trial. Patients with syphilitic aortitis should receive a full course of penicillin therapy. Beta blockers and the angiotensin receptor blocker losartan may be useful to retard the rate of aortic root

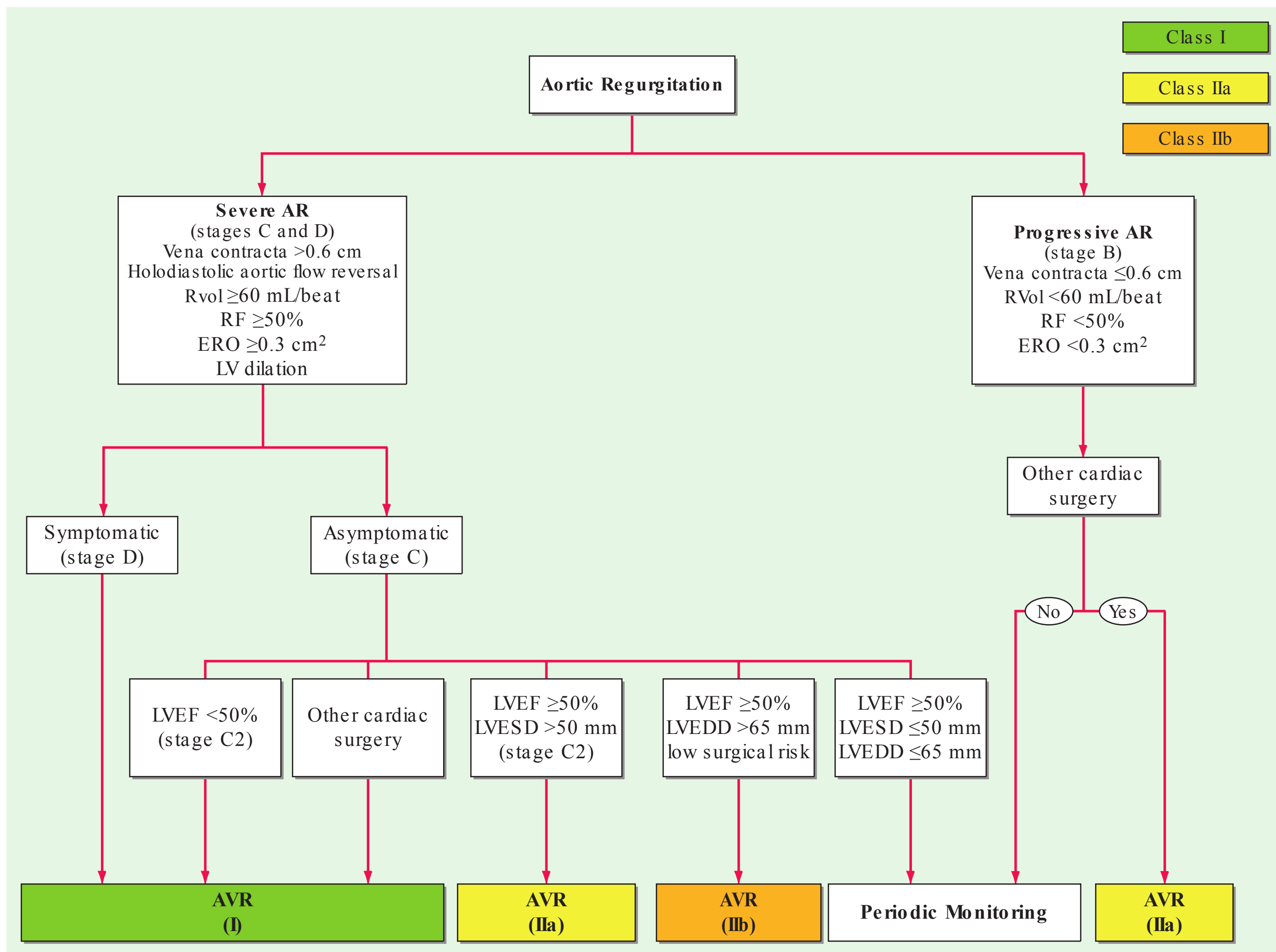


FIGURE 23-6

Management of patients with aortic regurgitation. See legend for Fig. 23-2 for explanation of treatment recommendations (Class I, IIa, and IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. AR, aortic

regurgitation; AVR, aortic valve replacement (valve repair may be appropriate in selected patients); ERO, effective regurgitant orifice; LV, left ventricular; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

enlargement in young patients with Marfan's syndrome and aortic root dilation. Early reports of the efficacy of losartan in patients with Marfan's syndrome have led to its use in other populations of patients including those with BAV disease and aortopathy. The use of beta blockers in patients with valvular AR was previously felt to be relatively contraindicated due to concerns that the resulting slowing of the heart rate would allow more time for diastolic regurgitation. More recent observational reports, however, suggest that beta blockers may provide functional benefit in patients with chronic AR. Beta blockers can sometimes provide incremental blood pressure lowering in patients with chronic AR and hypertension. Patients with severe AR, particularly those with an associated aortopathy, should avoid isometric exercises.

SURGICAL TREATMENT In deciding on the advisability and proper timing of surgical treatment, two points should be kept in mind: (1) patients with chronic severe AR usually do not become symptomatic until after the development of myocardial dysfunction; and (2) when delayed too long (defined as >1 year from onset of symptoms or LV dysfunction), surgical treatment often does not restore normal LV function. Therefore, in patients with chronic severe AR, careful clinical follow-up and noninvasive testing with echocardiography at approximately 6- to 12-month intervals are necessary if operation is to be undertaken at the optimal time, i.e., after the onset of LV dysfunction but prior to the development of severe symptoms. Exercise testing may be helpful to assess effort tolerance more objectively. Operation can be deferred

272 as long as the patient both remains asymptomatic and retains normal LV function without severe chamber dilation.

AVR is indicated for the treatment of severe AR in symptomatic patients irrespective of LV function. In general, the operation should be carried out in asymptomatic patients with severe AR and progressive LV dysfunction defined by an LVEF <50%, an LV end-systolic dimension >50 mm, or an LV diastolic dimension >65 mm. Smaller dimensions may be appropriate thresholds in individuals of smaller stature. Patients with severe AR without indications for operation should be followed by clinical and echocardiographic examination every 6–12 months.

Surgical options for management of aortic valve and root disease have expanded considerably over the past decade. AVR with a suitable mechanical or tissue prosthesis

is generally necessary in patients with rheumatic AR and in many patients with other forms of regurgitation. Rarely, when a leaflet has been perforated during infective endocarditis or torn from its attachments to the aortic annulus by thoracic trauma, primary surgical repair may be possible. When AR is due to aneurysmal dilation of the root or proximal ascending aorta rather than to primary valve involvement, it may be possible to reduce or eliminate the regurgitation by narrowing the annulus or by excising a portion of the aortic root without replacing the valve. Elective, valve-sparing aortic root reconstruction generally involves reimplantation of the valve in a contoured graft with reattachment of the coronary artery buttons into the side of the graft and is best undertaken in specialized surgical centers (**Fig. 23-7**). Resuspension of the native aortic valve leaflets is

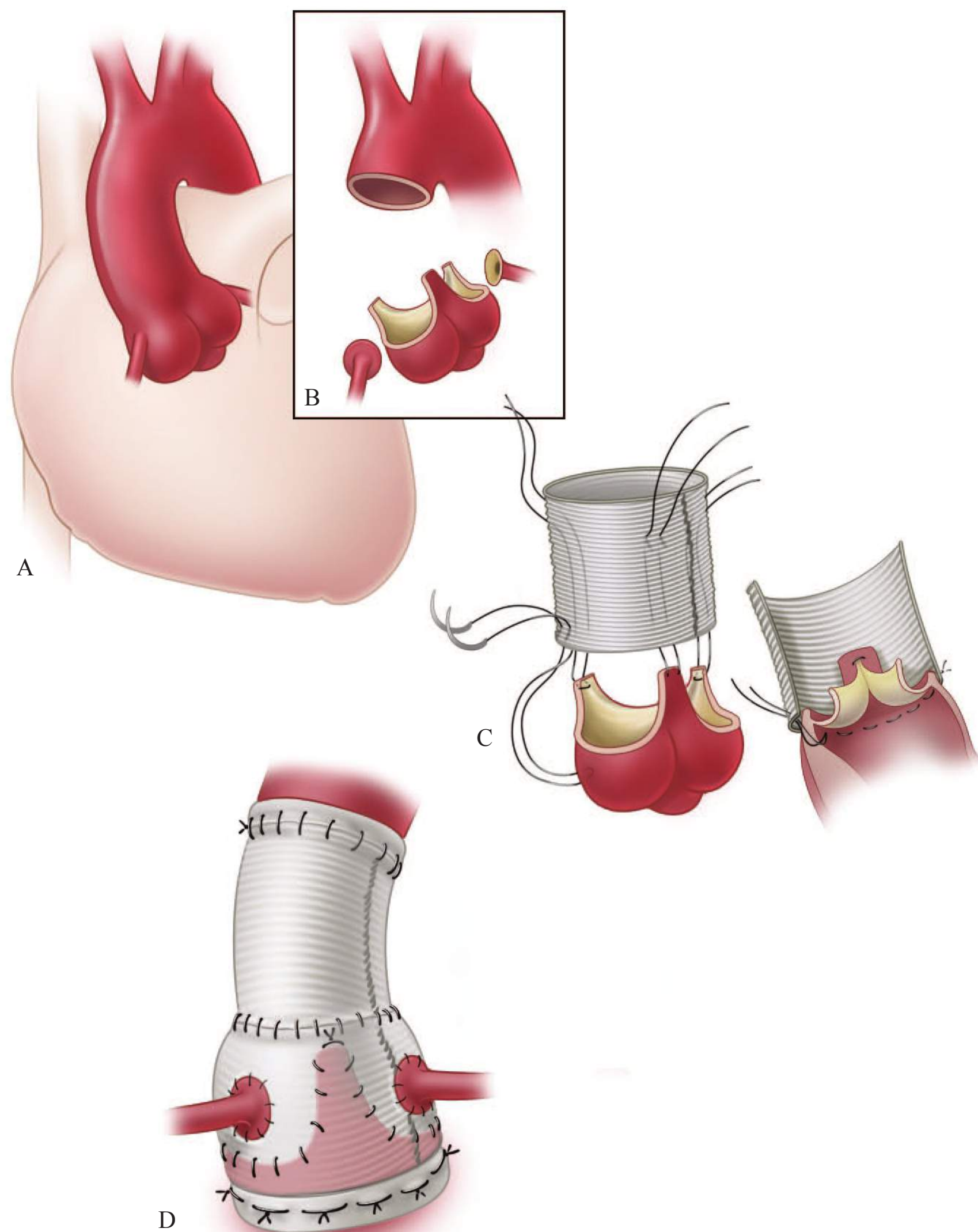


FIGURE 23-7

Valve-sparing aortic root reconstruction (David procedure). (From P Steltzer et al [eds]: Valvular

Heart Disease: A Companion to Braunwald's Heart Disease, 3rd ed, Fig 12-27, p. 200.)

possible in approximately 50% of patients with acute AR in the setting of type A aortic dissection. In other conditions, however, regurgitation can be effectively eliminated only by replacing the aortic valve, the dilated or aneurysmal ascending aorta responsible for the regurgitation, and implanting a composite valve-graft conduit. This formidable procedure entails a higher risk than isolated AVR.

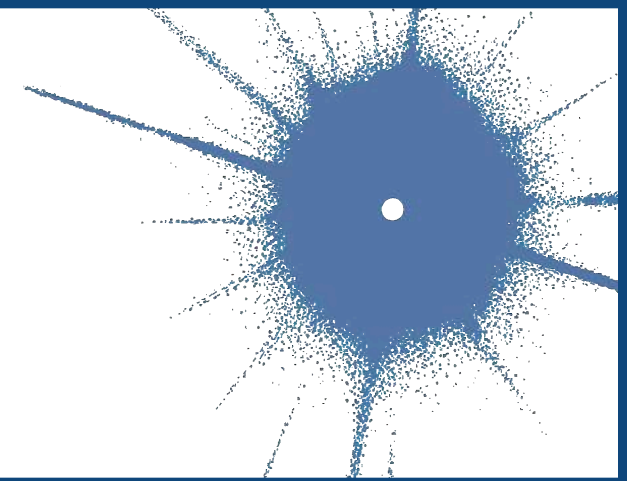
As in patients with other valvular abnormalities, both the operative risk and the late mortality rate are largely dependent on the stage of the disease and myocardial function at the time of operation. The overall operative mortality rate for isolated AVR (performed for either or both AS or AR) is

approximately 2% (Table 23-2). However, patients with AR, marked cardiac enlargement, and prolonged LV dysfunction experience an operative mortality rate of approximately 10% and a late mortality rate of approximately 5% per year due to LV failure despite a technically satisfactory operation. Nonetheless, because of the very poor prognosis with medical management, even patients with LV systolic failure should be considered for operation.

Patients with acute severe AR require prompt surgical treatment, which may be lifesaving.

CHAPTER 24

MITRAL VALVE DISEASE



Patrick T. O’Gara ■ Joseph Loscalzo

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in **Chaps. 9 and 10**; of electrocardiography (ECG) in **Chap. 11**; of echocardiography and other noninvasive imaging techniques in **Chap. 12**; and of cardiac catheterization and angiography in **Chap. 13**.

MITRAL STENOSIS

ETIOLOGY AND PATHOLOGY

Rheumatic fever is the leading cause of mitral stenosis (MS) (**Table 24-1**). Other less common etiologies of obstruction to left ventricular inflow include congenital mitral valve stenosis, cor triatriatum, mitral annular calcification with extension onto the leaflets, systemic lupus erythematosus, rheumatoid arthritis, left atrial myxoma, and infective endocarditis with large vegetations. Pure or predominant MS occurs in approximately 40% of all patients with rheumatic heart disease and a history of rheumatic fever (**Chap. 32**). In other patients with rheumatic heart disease, lesser degrees of MS may accompany mitral regurgitation (MR) and aortic valve disease. With reductions in the incidence of acute rheumatic fever, particularly in temperate climates and developed countries, the incidence of MS has declined considerably over the past several decades. However, it remains a major problem in developing nations, especially in tropical and semitropical climates.

In rheumatic MS, chronic inflammation leads to diffuse thickening of the valve leaflets with formation of fibrous tissue and/or calcific deposits. The mitral commissures fuse, the chordae tendineae fuse and shorten, the valvular cusps become rigid, and these changes, in turn, lead to narrowing at the apex of the funnel-shaped (“fish-mouth”) valve. Although the initial insult to the mitral valve is rheumatic, later changes may be exacerbated by a nonspecific process resulting from

trauma to the valve due to altered flow patterns. Calcification of the stenotic mitral valve immobilizes the leaflets and narrows the orifice further. Thrombus formation and arterial embolization may arise from the calcific valve itself, but in patients with atrial fibrillation (AF), thrombi arise more frequently from the dilated left atrium (LA), particularly from within the LA appendage.

PATHOPHYSIOLOGY

In normal adults, the area of the mitral valve orifice is 4–6 cm². In the presence of significant obstruction, i.e., when the orifice area is reduced to <~2 cm², blood can flow from the LA to the left ventricle (LV) only if propelled by an abnormally elevated left atrioventricular pressure gradient, the hemodynamic hallmark of MS. When the mitral valve opening is reduced to <1.5 cm², referred to as “severe” MS, an LA pressure of ~25 mmHg is required to maintain a normal cardiac output (CO). The elevated pulmonary venous and pulmonary arterial (PA) wedge pressures reduce pulmonary compliance, contributing to exertional dyspnea. The first bouts of dyspnea are usually precipitated by clinical events that increase the rate of blood flow across the mitral orifice, resulting in further elevation of the LA pressure (see below).

To assess the severity of obstruction hemodynamically, both the transvalvular pressure gradient and the flow rate must be measured (**Chap. 13**). The latter depends not only on the CO but on the heart rate, as well. An increase in heart rate shortens diastole proportionately more than systole and diminishes the time available for flow across the mitral valve. Therefore, at any given level of CO, tachycardia, including that associated with rapid AF, augments the transvalvular pressure gradient and elevates further the LA pressure. Similar considerations apply to the pathophysiology of tricuspid stenosis.

TABLE 24-1

MAJOR CAUSES OF MITRAL VALVE DISEASE	
VALVE LESION	ETIOLOGIES
Mitral stenosis	Rheumatic fever
	Congenital
	Severe mitral annular calcification
	SLE, RA
Mitral regurgitation	Acute
	Endocarditis
	Papillary muscle rupture (post-MI)
	Trauma
	Chordal rupture/leaflet flail (MVP, IE)
	Chronic
	Myxomatous (MVP)
	Rheumatic fever
	Endocarditis (healed)
	Mitral annular calcification
	Congenital (cleft, AV canal)
	HOCM with SAM
	Ischemic (LV remodeling)
	Dilated cardiomyopathy
	Radiation

Abbreviations: AV, atrioventricular; IE, infective endocarditis; HOCM, hypertrophic obstructive cardiomyopathy; LV, left ventricular; MI, myocardial infarction; MVP, mitral valve prolapse; RA, rheumatoid arthritis; SAM, systolic anterior motion; SLE, systemic lupus erythematosus.

The LV diastolic pressure and ejection fraction (EF) are normal in isolated MS. In MS and sinus rhythm, the elevated LA and PA wedge pressures exhibit a prominent atrial contraction pattern (a wave) and a gradual pressure decline after the v wave and mitral valve opening (y descent). In severe MS and whenever pulmonary vascular resistance is significantly increased, the PA pressure (PAP) is elevated at rest and rises further during exercise, often causing secondary elevations of right ventricular (RV) end-diastolic pressure and volume.

Cardiac output

In patients with severe MS (mitral valve orifice 1–1.5 cm²), the CO is normal or almost so at rest, but rises subnormally during exertion. In patients with very severe MS (valve area <1 cm²), particularly those in whom pulmonary vascular resistance is markedly elevated, the CO is subnormal at rest and may fail to rise or may even decline during activity.

Pulmonary hypertension

The clinical and hemodynamic features of MS are influenced importantly by the level of the PAP. Pulmonary hypertension results from: (1) passive backward transmission of the elevated LA pressure; (2) pulmonary arteriolar constriction (the so-called “second stenosis”), which presumably is triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension); (3) interstitial edema in the walls of the small pulmonary vessels; and (4) at end stage, organic obliterative changes in the pulmonary vascular bed. Severe pulmonary hypertension results in RV enlargement, secondary tricuspid regurgitation (TR), and pulmonic regurgitation (PR), as well as right-sided heart failure.

SYMPTOMS

In temperate climates, the latent period between the initial attack of rheumatic carditis (in the increasingly rare circumstances in which a history of one can be elicited) and the development of symptoms due to MS is generally about two decades; most patients begin to experience disability in the fourth decade of life. Studies carried out before the development of mitral valvotomy revealed that once a patient with MS became seriously symptomatic, the disease progressed inexorably to death within 2–5 years.

In patients whose mitral orifices are large enough to accommodate a normal blood flow with only mild elevations of LA pressure, marked elevations of this pressure leading to dyspnea and cough may be precipitated by sudden changes in the heart rate, volume status, or CO, as, for example, with severe exertion, excitement, fever, severe anemia, paroxysmal AF and other tachycardias, sexual intercourse, pregnancy, and thyrotoxicosis. As MS progresses, lesser degrees of stress precipitate dyspnea, the patient becomes limited in daily activities, and orthopnea and paroxysmal nocturnal dyspnea develop. The development of persistent AF often marks a turning point in the patient's course and is generally associated with acceleration of the rate at which symptoms progress. Hemoptysis results from rupture of pulmonary-bronchial venous connections secondary to pulmonary venous hypertension. It occurs most frequently in patients who have elevated LA pressures without markedly elevated pulmonary vascular resistances and is rarely fatal. Recurrent pulmonary emboli (**Chap. 45**), sometimes with infarction, are an important cause of morbidity and mortality late in the course of MS. Pulmonary infections, i.e., bronchitis, bronchopneumonia, and lobar pneumonia, commonly complicate untreated MS, especially during the winter months.

Pulmonary changes

In addition to the aforementioned changes in the pulmonary vascular bed, fibrous thickening of the walls of the alveoli and pulmonary capillaries occurs commonly in MS. The vital capacity, total lung capacity, maximal breathing capacity, and oxygen uptake per unit of ventilation are reduced. Pulmonary compliance falls further as pulmonary capillary pressure rises during exercise.

Thrombi and emboli

Thrombi may form in the left atria, particularly within the enlarged atrial appendages of patients with MS. Systemic embolization, the incidence of which is 10–20%, occurs more frequently in patients with AF, in patients >65 years of age, and in those with a reduced CO. However, systemic embolization may be the presenting feature in otherwise asymptomatic patients with only mild MS.

PHYSICAL FINDINGS

(See also Chaps. 9 and 10)

Inspection and palpation

In patients with severe MS, there may be a malar flush with pinched and blue facies. In patients with sinus rhythm and severe pulmonary hypertension or associated tricuspid stenosis (TS), the jugular venous pulse reveals prominent a waves due to vigorous right atrial systole. The systemic arterial pressure is usually normal or slightly low. An RV tap along the left sternal border signifies an enlarged RV. A diastolic thrill may rarely be present at the cardiac apex, with the patient in the left lateral recumbent position.

Auscultation

The first heart sound (S_1) is usually accentuated in the early stages of the disease and slightly delayed. The pulmonary component of the second heart sound (P_2) also is often accentuated with elevated PA pressures, and the two components of the second heart sound (S_2) are closely split. The opening snap (OS) of the mitral valve is most readily audible in expiration at, or just medial to, the cardiac apex. This sound generally follows the sound of aortic valve closure (A_2) by 0.05–0.12 s. The time interval between A_2 and OS varies inversely with the severity of the MS. The OS is followed by a low-pitched, rumbling, diastolic murmur, heard best at the apex with the patient in the left lateral recumbent position (see Fig. 9-5); it is accentuated by mild exercise (e.g., a few rapid sit-ups) carried out just before auscultation. In general, the duration of this murmur correlates with the severity of the stenosis in patients with

preserved CO. In patients with sinus rhythm, the murmur often reappears or becomes louder during atrial systole (presystolic accentuation). Soft, grade I or II/VI systolic murmurs are commonly heard at the apex or along the left sternal border in patients with pure MS and do not necessarily signify the presence of MR. Hepatomegaly, ankle edema, ascites, and pleural effusion, particularly in the right pleural cavity, may occur in patients with MS and RV failure.

Associated lesions

With severe pulmonary hypertension, a pansystolic murmur produced by functional TR may be audible along the left sternal border. This murmur is usually louder during inspiration and diminishes during forced expiration (Carvallo's sign). When the CO is markedly reduced in MS, the typical auscultatory findings, including the diastolic rumbling murmur, may not be detectable (silent MS), but they may reappear as compensation is restored. The Graham Steell murmur of PR, a high-pitched, diastolic, decrescendo blowing murmur along the left sternal border, results from dilation of the pulmonary valve ring and occurs in patients with mitral valve disease and severe pulmonary hypertension. This murmur may be indistinguishable from the more common murmur produced by aortic regurgitation (AR), although it may increase in intensity with inspiration and is accompanied by a loud and often palpable P_2 .

LABORATORY EXAMINATION

ECG

In MS and sinus rhythm, the P wave usually suggests LA enlargement (see Fig. 11-8). It may become tall and peaked in lead II and upright in lead V_1 when severe pulmonary hypertension or TS complicates MS and right atrial (RA) enlargement occurs. The QRS complex is usually normal. However, with severe pulmonary hypertension, right axis deviation and RV hypertrophy are often present.

Echocardiogram

(See also Chap. 12) Transthoracic echocardiography (TTE) with color flow and spectral Doppler imaging provides critical information, including measurements of mitral inflow velocity during early (E wave) and late (A wave in patients in sinus rhythm) diastolic filling, estimates of the transvalvular peak and mean gradients and of the mitral orifice area, the presence and severity of any associated MR, the extent of leaflet calcification and restriction, the degree of distortion of the subvalvular apparatus, and the anatomic suitability for percutaneous mitral balloon valvotomy (percutaneous mitral

balloon valvuloplasty [PMBV]; see below). In addition, TTE provides an assessment of LV and RV function, chamber sizes, an estimation of the PAP based on the tricuspid regurgitant jet velocity, and an indication of the presence and severity of any associated valvular lesions, such as aortic stenosis and/or regurgitation. Transesophageal echocardiography (TEE) provides superior images and should be used when TTE is inadequate for guiding management decisions. TEE is especially indicated to exclude the presence of LA thrombus prior to PMBV. The performance of TTE with exercise to evaluate the mean mitral diastolic gradient and PA pressures can be very helpful in the evaluation of patients with MS when there is a discrepancy between the clinical findings and the resting hemodynamics.

Chest x-ray

The earliest changes are straightening of the upper left border of the cardiac silhouette, prominence of the main PAs, dilation of the upper lobe pulmonary veins, and posterior displacement of the esophagus by an enlarged LA. Kerley B lines are fine, dense, opaque, horizontal lines that are most prominent in the lower and mid-lung fields and that result from distention of interlobular septae and lymphatics with edema when the resting mean LA pressure exceeds approximately 20 mmHg.

DIFFERENTIAL DIAGNOSIS

Like MS, significant MR may also be associated with a prominent diastolic murmur at the apex due to increased antegrade transmitral flow, but in patients with isolated MR, this diastolic murmur commences slightly later than in patients with MS, and there is often clear-cut evidence of LV enlargement. An OS and increased P_2 are absent, and S_1 is soft or absent. An apical pansystolic murmur of at least grade III/VI intensity as well as an S_3 suggest significant MR. Similarly, the apical mid-diastolic murmur associated with severe AR (Austin Flint murmur) may be mistaken for MS but can be differentiated from it because it is not intensified in presystole and becomes softer with administration of amyl nitrite or other arterial vasodilators. TS, which occurs rarely in the absence of MS, may mask many of the clinical features of MS or be clinically silent; when present, the diastolic murmur of TS increases with inspiration and the y descent in the jugular venous pulse is delayed.

Atrial septal defect (**Chap. 22**) may be mistaken for MS; in both conditions, there is often clinical, ECG, and chest x-ray evidence of RV enlargement and accentuation of pulmonary vascularity. However, the absence of LA enlargement and of Kerley B lines and the demonstration of fixed splitting of S_2 with a grade II or III mid-systolic murmur at the mid to upper left sternal

border all favor atrial septal defect over MS. Atrial septal defects with large left-to-right shunts may result in functional TS because of the enhanced diastolic flow.

Left atrial myxoma (**Chap. 29**) may obstruct LA emptying, causing dyspnea, a diastolic murmur, and hemodynamic changes resembling those of MS. However, patients with an LA myxoma often have features suggestive of a systemic disease, such as weight loss, fever, anemia, systemic emboli, and elevated serum IgG and interleukin 6 (IL-6) concentrations. The auscultatory findings may change markedly with body position. The diagnosis can be established by the demonstration of a characteristic echo-producing mass in the LA with TTE.

CARDIAC CATHETERIZATION

Left and right heart catheterization can be useful when there is a discrepancy between the clinical and noninvasive findings, including those from TEE and exercise echocardiographic testing as appropriate. Catheterization is helpful in assessing associated lesions, such as aortic stenosis (AS) and AR. Catheterization and coronary angiography are not usually necessary to aid in decision-making about surgery in patients younger than 65 years of age with typical findings of severe mitral obstruction on physical examination and TTE. In men older than 40 years of age, women older than 45 years of age, and younger patients with coronary risk factors, especially those with positive noninvasive stress tests for myocardial ischemia, coronary angiography is advisable preoperatively to identify patients with critical coronary obstructions that should be bypassed at the time of operation. Computed tomographic coronary angiography (CTCA) (**Chap. 12**) is now often used to screen preoperatively for the presence of coronary artery disease (CAD) in patients with valvular heart disease and low pretest likelihood of CAD. Catheterization and left ventriculography may be useful in patients who have undergone PMBV or previous mitral valve surgery for MS, and who have redeveloped limiting symptoms, especially if questions regarding the severity of the valve lesion(s) remain after noninvasive study.

TREATMENT MITRAL STENOSIS

(**Fig. 24-1**) Penicillin prophylaxis of group A β -hemolytic streptococcal infections (**Chap. 32**) for secondary prevention of rheumatic fever is important for at-risk patients with rheumatic MS. Recommendations for infective endocarditis prophylaxis are similar to those for other valve lesions and are restricted to patients at high risk for complications from infection, including patients with a history of endocarditis. In symptomatic patients, some improvement usually occurs with restriction of sodium intake and small doses of oral diuretics. Beta blockers, nondihydropyridine calcium

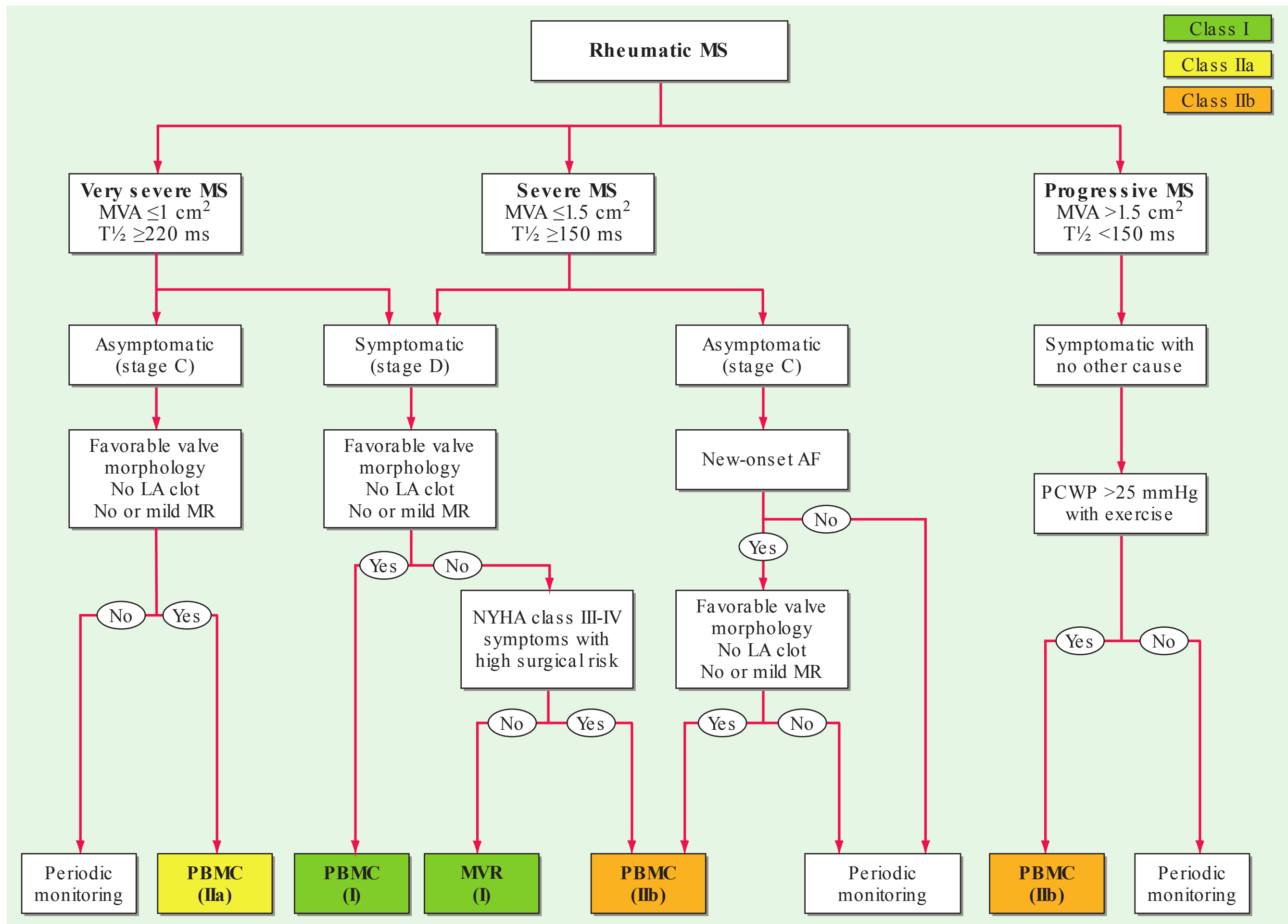


FIGURE 24-1

Management of rheumatic mitral stenosis. See legend for Fig. 24-2 for explanation of treatment recommendations (class I, IIa, IIb) and disease stages (C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral

stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and $T_{1/2}$, pressure half-time. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

channel blockers (e.g., verapamil or diltiazem), and digitalis glycosides are useful in slowing the ventricular rate of patients with AF. Warfarin therapy targeted to an international normalized ratio (INR) of 2–3 should be administered indefinitely to patients with MS who have AF or a history of thromboembolism. The routine use of warfarin in patients in sinus rhythm with LA enlargement (maximal dimension >5.5 cm) with or without spontaneous echo contrast is more controversial. The novel oral anticoagulants are not approved for use in patients with significant valvular heart disease.

If AF is of relatively recent onset in a patient whose MS is not severe enough to warrant PMBV or surgical commissurotomy, reversion to sinus rhythm pharmacologically or by means of electrical countershock is indicated. Usually, cardioversion should be undertaken after the patient has had

at least 3 consecutive weeks of anticoagulant treatment to a therapeutic INR. If cardioversion is indicated more urgently, then intravenous heparin should be provided and TEE performed to exclude the presence of LA thrombus before the procedure. Conversion to sinus rhythm is rarely successful or sustained in patients with severe MS, particularly those in whom the LA is especially enlarged or in whom AF has been present for more than 1 year.

MITRAL VALVOTOMY Unless there is a contraindication, mitral valvotomy is indicated in symptomatic (New York Heart Association [NYHA] Functional Class II–IV) patients with isolated severe MS, whose effective orifice (valve area) is < ~1 cm²/m² body surface area, or <1.5 cm² in normal-sized adults. Mitral valvotomy can be carried out by two techniques: PMBV and

surgical valvotomy. In PMBV (Figs. 24-2 and 24-3), a catheter is directed into the LA after transseptal puncture, and a single balloon is directed across the valve and inflated in the valvular orifice. Ideal patients have relatively pliable leaflets with little or no commissural calcium. In addition, the subvalvular structures should not be significantly scarred or thickened, and there should be no LA thrombus. The short- and long-term results of this procedure in appropriate patients are similar to those of surgical valvotomy, but with less morbidity and a lower peri-procedural mortality rate. Event-free survival in younger (<45 years) patients with pliable valves is excellent, with rates as high as 80–90% over 3–7 years. Therefore, PMBV has become the procedure of choice for such patients when it can be performed by a skilled operator in a high-volume center.

TTE is helpful in identifying patients for the percutaneous procedure, and TEE is performed routinely to exclude LA thrombus and to assess the degree of MR at the time of the scheduled procedure. An “echo score” has been developed to help guide decision-making. The score accounts for the degree of leaflet thickening, calcification, and mobility, and for the extent of subvalvular thickening. A lower score predicts a higher likelihood of successful PMBV.

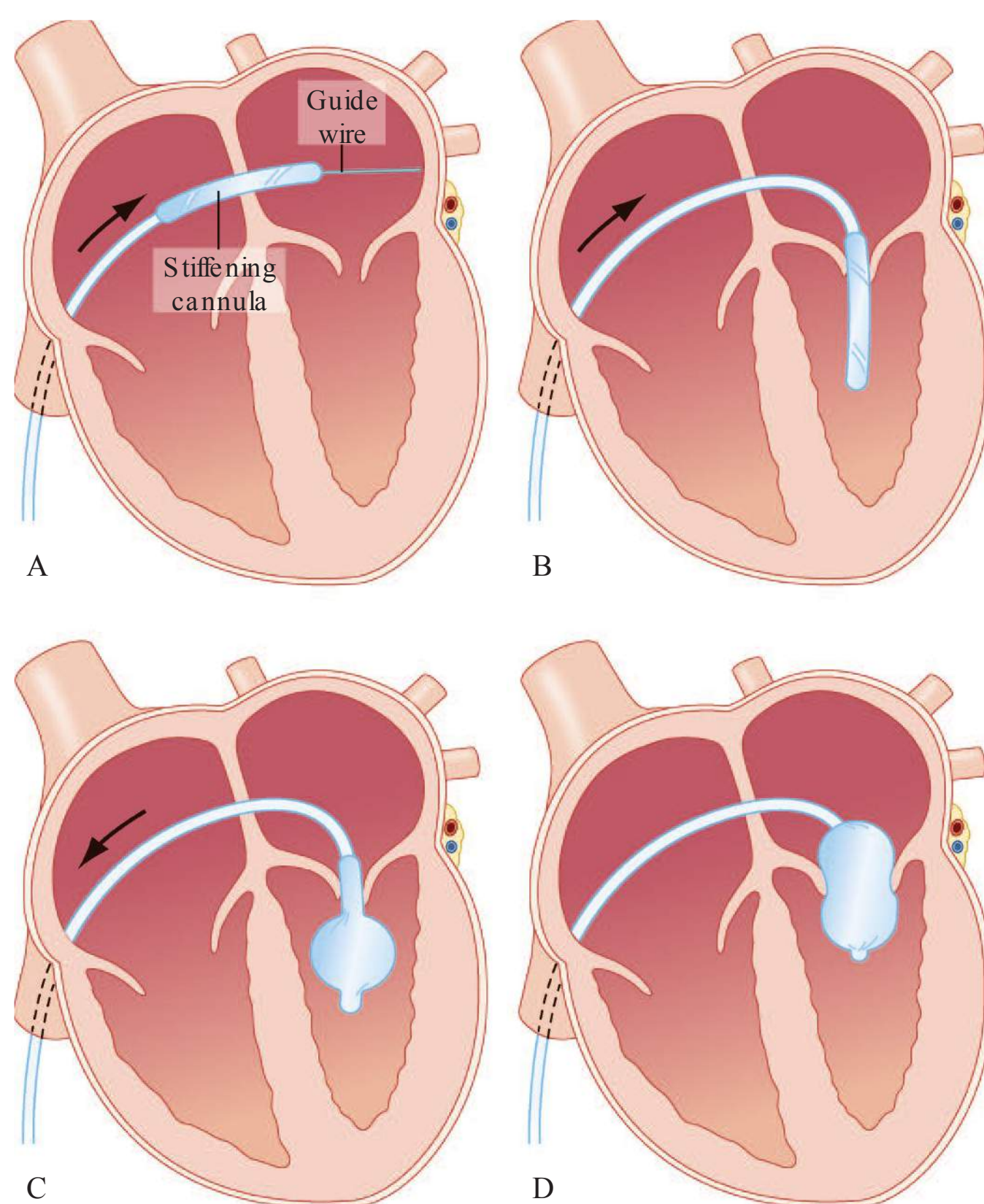


FIGURE 24-2

Inoue balloon technique for percutaneous mitral balloon valvotomy. A. After transseptal puncture, the deflated balloon catheter is advanced across the interatrial septum, then across the mitral valve and into the left ventricle. B–D. The balloon is inflated stepwise within the mitral orifice.

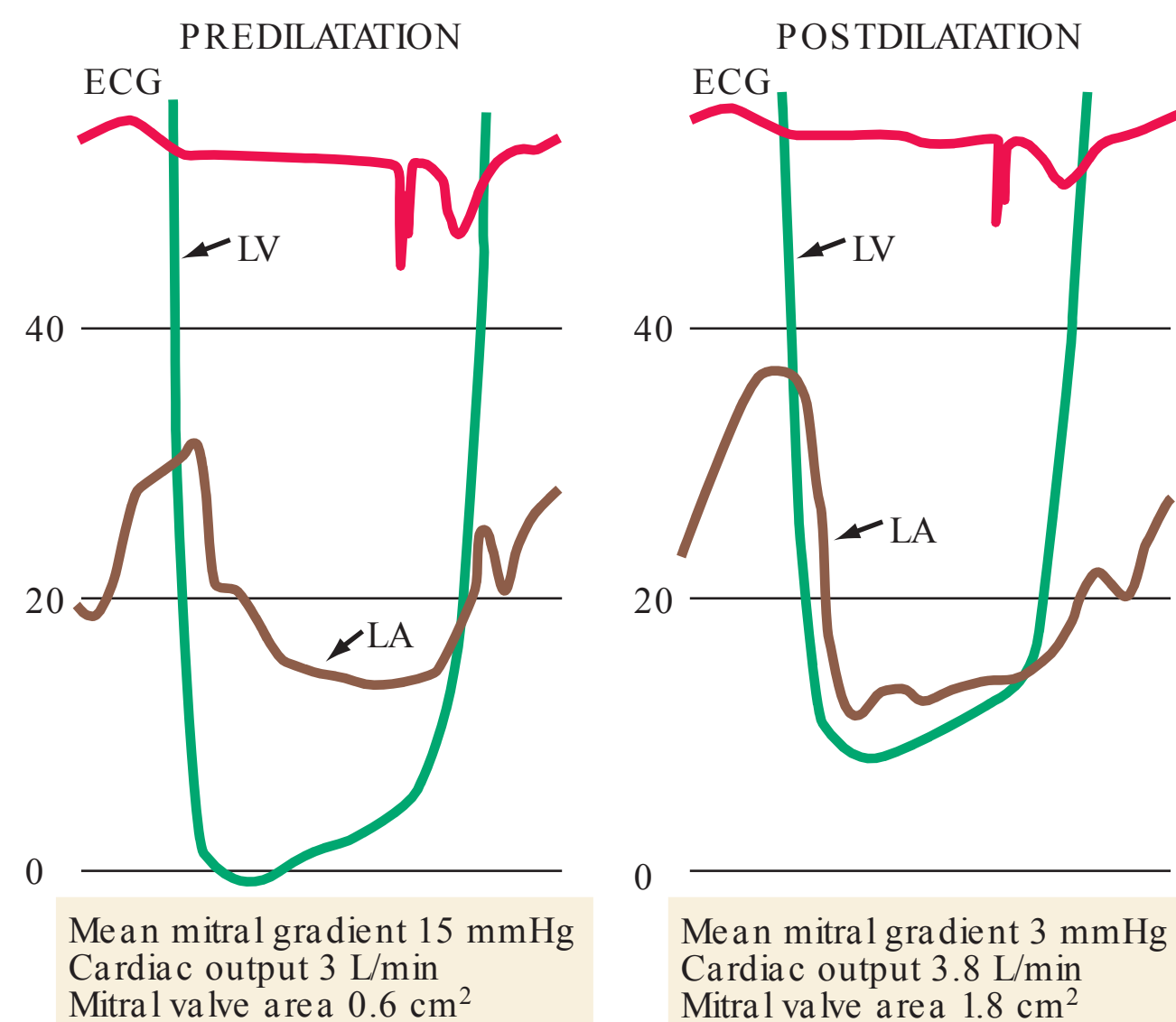


FIGURE 24-3

Simultaneous left atrial (LA) and left ventricular (LV) pressure before and after percutaneous mitral balloon valvuloplasty (PMBV) in a patient with severe mitral stenosis. ECG, electrocardiogram. (Courtesy of Raymond G. McKay, MD; with permission.)

In patients in whom PMBV is not possible or unsuccessful, or in many patients with restenosis after previous surgery, an “open” valvotomy using cardiopulmonary bypass is necessary. In addition to opening the valve commissures, it is important to loosen any subvalvular fusion of papillary muscles and chordae tendineae; to remove large deposits of calcium, thereby improving valvular function; and to remove atrial thrombi. The perioperative mortality rate is ~2%.

Successful valvotomy is defined by a 50% reduction in the mean mitral valve gradient and a doubling of the mitral valve area. Successful valvotomy, whether balloon or surgical, usually results in striking symptomatic and hemodynamic improvement and prolongs survival. However, there is no evidence that the procedure improves the prognosis of patients with slight or no functional impairment. Therefore, unless recurrent systemic embolization or severe pulmonary hypertension has occurred (PA systolic pressures >50 mmHg at rest or >60 mmHg with exercise), valvotomy is not recommended for patients who are entirely asymptomatic and/or who have mild or moderate stenosis (mitral valve area >1.5 cm²). When there is little symptomatic improvement after valvotomy, it is likely that the procedure was ineffective, that it induced MR, or that associated valvular or myocardial disease was present. About half of all patients undergoing surgical mitral valvotomy require reoperation by 10 years. In the pregnant patient with MS, valvotomy should be carried out if pulmonary congestion occurs despite intensive medical treatment. PMBV is the preferred strategy in this setting and is performed with TEE and no or minimal x-ray exposure.

Mitral valve replacement (MVR) is necessary in patients with MS and significant associated MR, those in whom the

TABLE 24-2
MORTALITY RATES AFTER MITRAL VALVE SURGERY^a

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
MVR(isolated)	3154	5.2
MVR+ CAB	1184	10.0
MVRp	4215	1.0
MVRp + CAB	2330	4.8

^aData are for the first two quarters of calendar year 2013, during which 1004 sites reported a total of 135,666 procedures. Data are available from the Society of Thoracic Surgeons at http://www.sts.org/sites/default/files/documents/2013_3rdHarvestExecutiveSummary.pdf.
Abbreviations: CAB, coronary artery bypass; MVR, mitral valve replacement; MVRp, mitral valve repair.

valve has been severely distorted by previous transcatheter or operative manipulation, or those in whom the surgeon does not find it possible to improve valve function significantly with valvotomy. MVR is now routinely performed with preservation of the chordal attachments to optimize LV functional recovery. Perioperative mortality rates with MVR vary with age, LV function, the presence of CAD, and associated comorbidities. They average 5% overall but are lower in young patients and may be twice as high in patients >65 years of age with significant comorbidities (Table 24-2). Because there are also long-term complications of valve replacement, patients in whom preoperative evaluation suggests the possibility that MVR may be required should be operated on only if they have severe MS—i.e., an orifice area $\leq 1.5\text{ cm}^2$ —and are in NYHA Class III, i.e., symptomatic with ordinary activity despite optimal medical therapy. The overall 10-year survival of surgical survivors is ~70%. Long-term prognosis is worse in patients >65 years of age and those with marked disability and marked depression of the CO preoperatively. Pulmonary hypertension and RV dysfunction are additional risk factors for poor outcome.

MITRAL REGURGITATION

ETIOLOGY

MR may result from an abnormality or disease process that affects any one or more of the five functional components of the mitral valve apparatus (leaflets, annulus, chordae tendineae, papillary muscles, and subjacent myocardium) (Table 24-1). Acute MR can occur in the setting of acute myocardial infarction (MI) with papillary muscle rupture (Chap. 41), following blunt chest wall trauma, or during the course of infective endocarditis. With acute MI, the posteromedial papillary muscle is involved much more frequently than the anterolateral papillary muscle because of its singular blood supply. Transient, acute MR can occur during periods of active ischemia and bouts of

angina pectoris. Rupture of chordae tendineae can result in “acute-on-chronic MR” in patients with myxomatous degeneration of the valve apparatus.

Chronic MR can result from rheumatic disease, mitral valve prolapse (MVP), extensive mitral annular calcification, congenital valve defects, hypertrophic obstructive cardiomyopathy (HOCM), and dilated cardiomyopathy (Chap. 27). Distinction also should be drawn between primary (degenerative, organic) MR, in which the leaflets and/or chordae tendineae are primarily responsible for abnormal valve function, and functional (secondary) MR, in which the leaflets and chordae tendineae are structurally normal but the regurgitation is caused by annular enlargement, papillary muscle displacement, leaflet tethering, or their combination. The rheumatic process produces rigidity, deformity, and retraction of the valve cusps and commissural fusion, as well as shortening, contraction, and fusion of the chordae tendineae. The MR associated with both MVP and HOCM is usually dynamic in nature. MR in HOCM occurs as a consequence of anterior papillary muscle displacement and systolic anterior motion of the anterior mitral valve leaflet into the narrowed LV outflow tract. Annular calcification is especially prevalent among patients with advanced renal disease and is commonly observed in women >65 years of age with hypertension and diabetes. MR may occur as a congenital anomaly (Chap. 22), most commonly as a defect of the endocardial cushions (atrioventricular cushion defects). A cleft anterior mitral valve leaflet accompanies primum atrial septal defect. Chronic MR is frequently secondary to ischemia and may occur as a consequence of ventricular remodeling, papillary muscle displacement, and leaflet tethering, or with fibrosis of a papillary muscle, in patients with healed MI(s) and ischemic cardiomyopathy. Similar mechanisms of annular dilation and ventricular remodeling contribute to the MR that occurs among patients with nonischemic forms of dilated cardiomyopathy once the LV end-diastolic dimension reaches 6 cm.

Irrespective of cause, chronic severe MR is often progressive, because enlargement of the LA places tension on the posterior mitral leaflet, pulling it away from the mitral orifice and thereby aggravating the valvular dysfunction. Similarly, LV dilation increases the regurgitation, which, in turn, enlarges the LA and LV further, resulting in a vicious circle; hence the aphorism, “mitral regurgitation begets mitral regurgitation.”

PATHOPHYSIOLOGY

The resistance to LV emptying (LV afterload) is reduced in patients with MR. As a consequence, the LV is decompressed into the LA during ejection, and with the reduction in LV size during systole, there is a rapid decline in LV tension. The initial compensation to MR

is more complete LV emptying. However, LV volume increases progressively with time as the severity of the regurgitation increases and as LV contractile function deteriorates. This increase in LV volume is often accompanied by a reduced forward CO. LV compliance is often increased, and thus, LV diastolic pressure does not increase until late in the course. The regurgitant volume varies directly with the LV systolic pressure and the size of the regurgitant orifice; the latter, in turn, is influenced by the extent of LV and mitral annular dilation. Because EF rises in severe MR in the presence of normal LV function, even a modest reduction in this parameter (<60%) reflects significant dysfunction.

During early diastole, as the distended LA empties, there is a particularly rapid y descent in the absence of accompanying MS. A brief, early diastolic LA-LV pressure gradient (often generating a rapid filling sound [S_3] and mid-diastolic murmur masquerading as MS) may occur in patients with pure, severe MR as a result of the very rapid flow of blood across a normal-sized mitral orifice.

Semiquantitative estimates of LV ejection fraction (LVEF), CO, PA systolic pressure, regurgitant volume, regurgitant fraction (RF), and the effective regurgitant orifice area can be obtained during a careful Doppler echocardiographic examination. These measurements can also be obtained accurately with cardiac magnetic resonance (CMR) imaging, although this technology is not widely available. Left and right heart catheterization with contrast ventriculography is used less frequently. Severe, nonischemic MR is defined by a regurgitant volume ≥ 60 mL/beat, RF $\geq 50\%$, and effective regurgitant orifice area ≥ 0.40 cm². Severe ischemic MR, however, is usually associated with an effective regurgitant orifice area of >0.2 cm². In the latter instance, lesser degrees of MR carry relatively greater prognostic weight.

LA compliance

In acute severe MR, the regurgitant volume is delivered into a normal-sized LA having normal or reduced compliance. As a result, LA pressures rise markedly for any increase in LA volume. The v wave in the LA pressure pulse is usually prominent, LA and pulmonary venous pressures are markedly elevated, and pulmonary edema is common. Because of the rapid rise in LA pressures during ventricular systole, the murmur of acute MR is early in timing and decrescendo in configuration ending well before S_2 , as a reflection of the progressive diminution in the LV-LA pressure gradient. LV systolic function in acute MR may be normal, hyperdynamic, or reduced, depending on the clinical context.

Patients with chronic severe MR, on the other hand, develop marked LA enlargement and increased LA compliance with little if any increase in LA and pulmonary venous pressures for any increase in LA volume.

The LA v wave is relatively less prominent. The murmur of chronic MR is classically holosystolic in timing and plateau in configuration, as a reflection of the near-constant LV-LA pressure gradient. These patients usually complain of severe fatigue and exhaustion secondary to a low forward CO, whereas symptoms resulting from pulmonary congestion are less prominent initially; AF is almost invariably present once the LA dilates significantly.

SYMPTOMS

Patients with chronic mild-to-moderate, isolated MR are usually asymptomatic. This form of LV volume overload is well tolerated. Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic severe MR. Palpitations are common and may signify the onset of AF. Right-sided heart failure, with painful hepatic congestion, ankle edema, distended neck veins, ascites, and secondary TR, occurs in patients with MR who have associated pulmonary vascular disease and pulmonary hypertension. Acute pulmonary edema is common in patients with acute severe MR.

PHYSICAL FINDINGS

In patients with chronic severe MR, the arterial pressure is usually normal, although the carotid arterial pulse may show a sharp, low-volume upstroke owing to the reduced forward CO. A systolic thrill is often palpable at the cardiac apex, the LV is hyperdynamic with a brisk systolic impulse and a palpable rapid-filling wave (S_3), and the apex beat is often displaced laterally.

In patients with acute severe MR, the arterial pressure may be reduced with a narrow pulse pressure, the jugular venous pressure and wave forms may be normal or increased and exaggerated, the apical impulse is not displaced, and signs of pulmonary congestion are prominent.

Auscultation

S_1 is generally absent, soft, or buried in the holosystolic murmur of chronic, severe MR. In patients with severe MR, the aortic valve may close prematurely, resulting in wide but physiologic splitting of S_2 . A low-pitched S_3 occurring 0.12–0.17 s after the aortic valve closure sound, i.e., at the completion of the rapid-filling phase of the LV, is believed to be caused by the sudden tensing of the papillary muscles, chordae tendineae, and valve leaflets. It may be followed by a short, rumbling, mid-diastolic murmur, even in the absence of structural MS. A fourth heart sound is often audible in patients with acute severe MR who are in sinus rhythm. A presystolic murmur is not ordinarily heard with isolated MR.

A systolic murmur of at least grade III/VI intensity is the most characteristic auscultatory finding in chronic severe MR. It is usually holosystolic (see **Fig. 9-5A**), but as previously noted, it is decrescendo and ceases in mid to late systole in patients with acute severe MR. The systolic murmur of chronic MR is usually most prominent at the apex and radiates to the axilla. However, in patients with ruptured chordae tendineae or primary involvement of the posterior mitral leaflet with prolapse or flail, the regurgitant jet is eccentric, directed anteriorly, and strikes the LA wall adjacent to the aortic root. In this situation, the systolic murmur is transmitted to the base of the heart and, therefore, may be confused with the murmur of AS. In patients with ruptured chordae tendineae, the systolic murmur may have a cooing or “seagull” quality, whereas a flail leaflet may produce a murmur with a musical quality. The systolic murmur of chronic MR not due to MVP is intensified by isometric exercise (handgrip) but is reduced during the strain phase of the Valsalva maneuver because of the associated decrease in LV preload.

LABORATORY EXAMINATION

ECG

In patients with sinus rhythm, there is evidence of LA enlargement, but RA enlargement also may be present when pulmonary hypertension is significant and affects RV function. Chronic severe MR is frequently associated with AF. In many patients, there is no clear-cut ECG evidence of enlargement of either ventricle. In others, the signs of eccentric LV hypertrophy are present.

Echocardiogram

TTE is indicated to assess the mechanism of the MR and its hemodynamic severity. LV function can be assessed from LV end-diastolic and end-systolic volumes and EF. Observations can be made regarding leaflet structure and function, chordal integrity, LA and LV size, annular calcification, and regional and global LV systolic function. Doppler imaging should demonstrate the width or area of the color flow MR jet within the LA, the duration and intensity of the continuous wave Doppler signal, the pulmonary venous flow contour, the early peak mitral inflow velocity, and quantitative measures of regurgitant volume, RF, and effective regurgitant orifice area. In addition, the PAPs can be estimated from the TR jet velocity. TTE is also indicated to follow the course of patients with chronic MR and to provide rapid assessment for any clinical change. The echocardiogram in patients with MVP is described in the next section. TEE provides greater anatomic detail than TTE (see **Fig. 12-5**). Exercise testing with

TTE can be useful to assess exercise capacity as well as any dynamic change in MR severity, PA systolic pressures, and biventricular function, for patients in whom there is a discrepancy between clinical findings and the results of functional testing performed at rest.

Chest x-ray

The LA and LV are the dominant chambers in chronic MR. Late in the course of the disease, the LA may be massively enlarged and forms the right border of the cardiac silhouette. Pulmonary venous congestion, interstitial edema, and Kerley B lines are sometimes noted. Marked calcification of the mitral leaflets occurs commonly in patients with long-standing, combined rheumatic MR and MS. Calcification of the mitral annulus may be visualized, particularly on the lateral view of the chest. Patients with acute severe MR may have asymmetric pulmonary edema if the regurgitant jet is directed predominantly to the orifice of an upper lobe pulmonary vein.

TREATMENT Mitral Regurgitation

MEDICAL TREATMENT The management of chronic severe MR depends to some degree on its cause (**Fig. 24-4**). Warfarin should be provided once AF intervenes with a target INR of 2–3. Novel oral anticoagulants are not approved for this indication. Cardioversion should be considered depending on the clinical context and LA size. In contrast to the acute setting, there are no large, long-term prospective studies to substantiate the use of vasodilators for the treatment of chronic, isolated severe MR with preserved LV systolic function in the absence of systemic hypertension. The severity of MR in the setting of an ischemic or nonischemic dilated cardiomyopathy may diminish with aggressive guideline-directed treatment of heart failure including the use of diuretics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, digitalis, and biventricular pacing (cardiac resynchronization therapy [CRT]) when otherwise indicated. Asymptomatic patients with severe MR in sinus rhythm with normal LV size and systolic function should avoid isometric forms of exercise.

Patients with acute severe MR require urgent stabilization and preparation for surgery. Diuretics, intravenous vasodilators (particularly sodium nitroprusside), and even intraaortic balloon counterpulsation may be needed for patients with post-MI papillary muscle rupture or other forms of acute severe MR.

SURGICAL TREATMENT In the selection of patients with chronic, nonischemic, primary or organic, severe MR for surgical treatment, the often slowly progressive nature of the condition must be balanced against the immediate and long-term risks

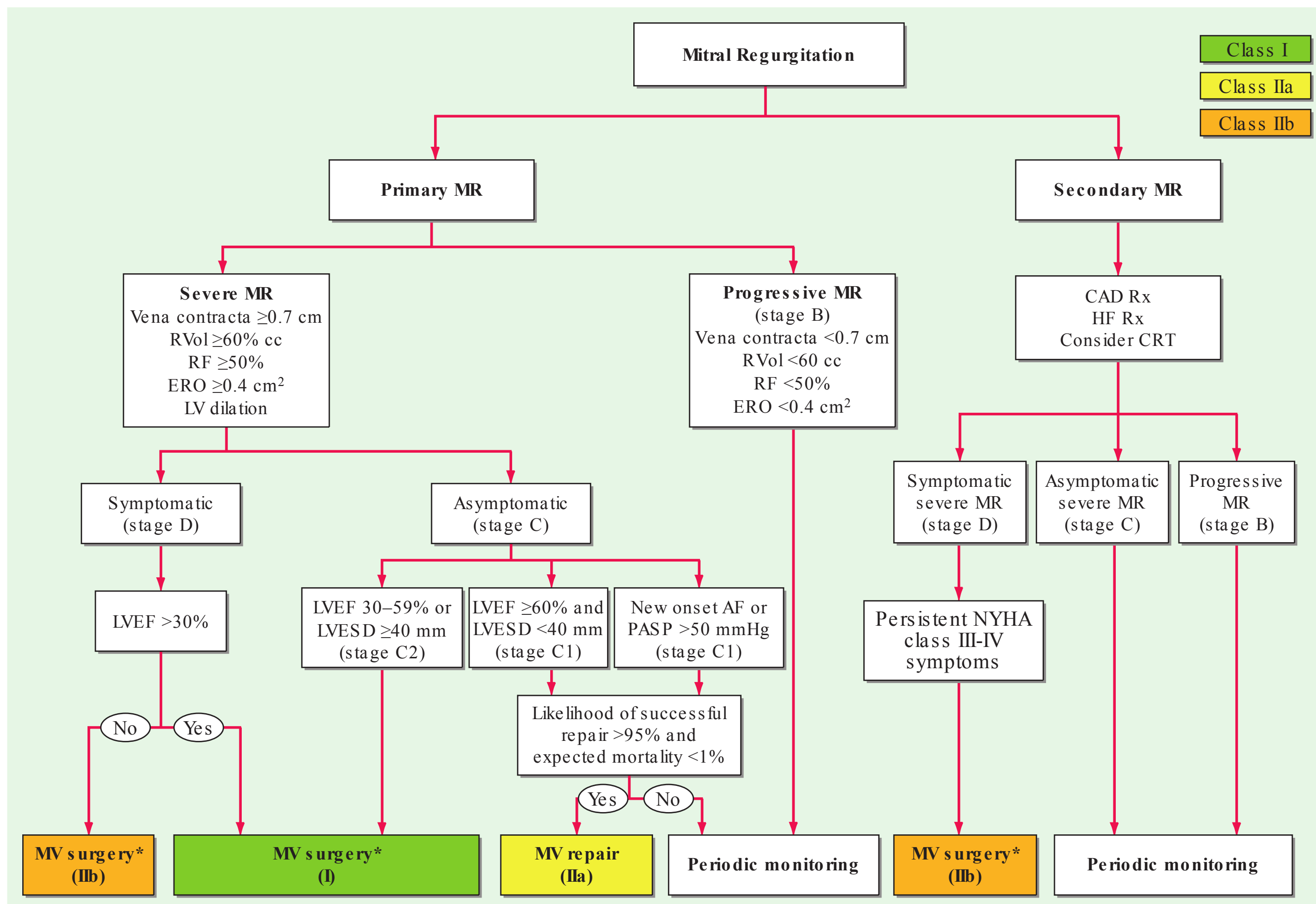


FIGURE 24-4

Management of mitral regurgitation. See legend for Fig. 23-2 for explanation of treatment recommendations (class I, IIa, IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LV,

left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy. [Mitral valve repair preferred over MVR when possible. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

associated with operation. These risks are significantly lower for primary valve repair than for valve replacement (Table 27-2). Repair usually consists of valve reconstruction using a variety of valvuloplasty techniques and insertion of an annuloplasty ring. Repair spares the patient the long-term adverse consequences of valve replacement, including thromboembolic and hemorrhagic complications in the case of mechanical prostheses and late valve failure necessitating repeat valve replacement in the case of bioprostheses. In addition, by preserving the integrity of the papillary muscles, subvalvular apparatus, and chordae tendineae, mitral repair and valvuloplasty maintain LV function to a relatively greater degree.

Surgery for chronic nonischemic severe MR is indicated once symptoms occur, especially if valve repair is feasible (Fig. 24-4). Other indications for early consideration of mitral valve repair include recent-onset AF and pulmonary hypertension defined as a systolic PA pressure ≥ 50 mmHg at rest

or ≥ 60 mmHg with exercise. Surgical treatment of chronic nonischemic severe MR is indicated for asymptomatic patients when LV dysfunction is progressive with the LVEF falling below 60% and/or end-systolic dimension increasing beyond 40 mm. These aggressive recommendations for surgery are predicated on the outstanding results achieved with mitral valve repair particularly when applied to patients with myxomatous disease such as that associated with prolapse or flail leaflet. Indeed primary valvuloplasty repair of patients younger than 75 years with normal LV systolic function and no CAD can now be performed by experienced surgeons with <1% perioperative mortality risk. The risk of stroke, however, is also approximately 1%. Repair is feasible in up to 95% of patients with myxomatous disease operated on by a high-volume surgeon in a referral center of excellence. Long-term durability is excellent; the incidence of reoperative surgery for failed primary repair is ~1% per year for the first 10 years after

surgery. For patients with AF, left or biatrial maze surgery, or radiofrequency, isolation of the pulmonary veins is often performed to reduce the risk of recurrent postoperative AF.

The surgical management of patients with functional, ischemic MR is more complicated and most often involves simultaneous coronary artery revascularization. Current surgical practice includes annuloplasty repair with an undersized, rigid ring or chord-sparing valve replacement for patients with moderate or greater degrees of MR. Valve repair for ischemic MR is associated with lower perioperative mortality rates but higher rates of recurrent MR over time. In patients with ischemic MR and significantly impaired LV systolic function ($EF < 30\%$), the risk of surgery is higher, recovery of LV performance is incomplete, and long-term survival is reduced. Referral for surgery must be individualized and made only after aggressive attempts with guideline-directed medical therapy and CRT, when indicated. The routine performance of valve repair in patients with significant MR in the setting of severe, functional, nonischemic dilated cardiomyopathy has not been shown to improve long-term survival compared with optimal medical therapy. Patients with acute severe MR can often be stabilized temporarily with appropriate medical therapy, but surgical correction will be necessary emergently in the case of papillary muscle rupture and within days to weeks in most other settings.

When surgical treatment is contemplated, left and right heart catheterization and left ventriculography may be helpful in confirming the presence of severe MR in patients in whom there is a discrepancy between the clinical and TTE findings that cannot be resolved with TEE or CMR. Coronary angiography identifies patients who require concomitant coronary revascularization.

TRANSCATHETER MITRAL VALVE REPAIR A transcatheter approach to the treatment of either organic or functional MR may be feasible in selected patients with appropriate anatomy. The proper role of currently available techniques remains under active investigation. One approach involves the deployment of a clip delivered via transseptal puncture that grasps the leading edges of the mitral leaflets in their midportion (anterior scallop to posterior scallop or A2-P2; **Fig. 24-5**). The length and width of the gap between these leading edges dictate patient eligibility. The device is commercially available for the treatment of prohibitive surgical risk patients with severe, degenerative (organic) MR and is undergoing study in the United States for treatment of patients with symptomatic heart failure, reduced LVEF, and severe, functional MR despite guideline-directed medical therapy. A second approach involves the deployment of a device within the coronary sinus that can be adjusted to reduce its circumference, thus secondarily decreasing the circumference of the mitral annulus and the effective orifice area of the valve much like a surgically implanted ring. Variations in the anatomic relationship of the coronary sinus to the mitral annulus and circumflex coronary artery have limited the applicability of this technique. Attempts



FIGURE 24-5

Clip used to grasp the free edges of the anterior and posterior leaflets in their midsections during transcatheter repair of selected patients with mitral regurgitation. (Courtesy of Abbott Vascular. © 2014 Abbott Laboratories. All rights reserved.)

to reduce the septal-lateral dimension of a dilated annulus using adjustable cords placed across the LV in a subvalvular location have also been investigated.

MITRAL VALVE PROLAPSE

MVP, also variously termed the systolic click-murmur syndrome, Barlow's syndrome, floppy-valve syndrome, and billowing mitral leaflet syndrome, is a relatively common but highly variable clinical syndrome resulting from diverse pathologic mechanisms of the mitral valve apparatus. Among these are excessive or redundant mitral leaflet tissue, which is commonly associated with myxomatous degeneration and greatly increased concentrations of certain glycosaminoglycans.

In most patients with MVP, the cause is unknown, but in some, it appears to be genetically determined. A reduction in the production of type III collagen has been incriminated, and electron microscopy has revealed fragmentation of collagen fibrils.

MVP is a frequent finding in patients with heritable disorders of connective tissue, including Marfan's syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome. MVP may be associated with thoracic skeletal deformities similar to but not as severe as those in Marfan's syndrome, such as a high-arched palate and alterations of the chest and thoracic spine, including the so-called straight back syndrome.

In most patients with MVP, myxomatous degeneration is confined to the mitral valve, although the tricuspid and aortic valves may also be affected. The posterior mitral leaflet is usually more affected than the anterior, and the mitral valve annulus is often dilated. In many

patients, elongated, redundant, or ruptured chordae tendineae cause or contribute to the regurgitation.

MVP also may occur rarely as a sequel to acute rheumatic fever, in ischemic heart disease, and in various cardiomyopathies, as well as in 20% of patients with ostium secundum atrial septal defect.

MVP may lead to excessive stress on the papillary muscles, which, in turn, leads to dysfunction and ischemia of the papillary muscles and the subjacent ventricular myocardium. Rupture of chordae tendineae and progressive annular dilation and calcification contribute to valvular regurgitation, which then places more stress on the diseased mitral valve apparatus, thereby creating a vicious circle. ECG changes (see below) and ventricular arrhythmias described in some patients with MVP appear to result from regional ventricular dysfunction related to the increased stress placed on the papillary muscles.

CLINICAL FEATURES

MVP is more common in women and occurs most frequently between the ages of 15 and 30 years; the clinical course is most often benign. MVP may also be observed in older (>50 years) patients, often men, in whom MR is often more severe and requires surgical treatment. There is an increased familial incidence for some patients, suggesting an autosomal dominant form of inheritance with incomplete penetrance. MVP varies in its clinical expression, ranging from only a systolic click and murmur with mild prolapse of the posterior leaflet to severe MR due to chordal rupture and leaflet flail. The degree of myxomatous change of the leaflets can also vary widely. In many patients, the condition progresses over years or decades; in others, it worsens rapidly as a result of chordal rupture or endocarditis.

Most patients are asymptomatic and remain so for their entire lives. However, in North America, MVP is now the most common cause of isolated severe MR requiring surgical treatment. Arrhythmias, most commonly ventricular premature contractions and paroxysmal supraventricular and ventricular tachycardia, as well as AF, have been reported and may cause palpitations, light-headedness, and syncope. Sudden death is a very rare complication and occurs most often in patients with severe MR and depressed LV systolic function. There may be an excess risk of sudden death among patients with a flail leaflet. Many patients have chest pain that is difficult to evaluate; it is often substernal, prolonged, and not related to exertion, but may rarely resemble angina pectoris. Transient cerebral ischemic attacks secondary to emboli from the mitral valve due to endothelial disruption have been reported. Infective endocarditis may occur in patients with MR and/or leaflet thickening.

Auscultation

A frequent finding is the mid or late (nonejection) systolic click, which occurs 0.14 s or more after S_1 and is thought to be generated by the sudden tensing of slack, elongated chordae tendineae or by the prolapsing mitral leaflet when it reaches its maximal excursion. Systolic clicks may be multiple and may be followed by a high-pitched, mid-late systolic crescendo-decrescendo murmur, which occasionally is “whooping” or “honking” and is heard best at the apex. The click and murmur occur earlier with standing, during the strain phase of the Valsalva maneuver, and with any intervention that decreases LV volume, exaggerating the propensity of mitral leaflet prolapse. Conversely, squatting and isometric exercises, which increase LV volume, diminish MVP; the click-murmur complex is delayed, moves away from S_1 , and may even disappear. Some patients have a mid-systolic click without a murmur; others have a murmur without a click. Still others have both sounds at different times.

LABORATORY EXAMINATION

The ECG most commonly is normal but may show biphasic or inverted T waves in leads II, III, and aVF, and occasionally supraventricular or ventricular premature beats. TTE is particularly effective in identifying the abnormal position and prolapse of the mitral valve leaflets. A useful echocardiographic definition of MVP is systolic displacement (in the parasternal long axis view) of the mitral valve leaflets by at least 2 mm into the LA superior to the plane of the mitral annulus. Color flow and continuous wave Doppler imaging is helpful to evaluate the associated MR and provide semi-quantitative estimates of severity. The jet lesion of MR due to MVP is most often eccentric, and assessment of RF and effective regurgitant orifice area can be difficult. TEE is indicated when more accurate information is required and is performed routinely for intraoperative guidance for valve repair. Invasive left ventriculography is rarely necessary but can also show prolapse of the posterior and sometimes of both mitral valve leaflets.

TREATMENT Mitral Valve Prolapse

Infective endocarditis prophylaxis is indicated only for patients with a prior history of endocarditis. Beta blockers sometimes relieve chest pain and control palpitations. If the patient is symptomatic from severe MR, mitral valve repair (or rarely, chord-sparing replacement) is indicated (Fig. 24-4). Antiplatelet agents, such as aspirin, should be given to patients with transient ischemic attacks, and if these are not effective, warfarin should be considered. Warfarin is also indicated once AF intervenes.

CHAPTER 25

TRICUSPID AND PULMONIC VALVE DISEASE



Patrick T. O’Gara ■ Joseph Loscalzo

TRICUSPID STENOSIS

Tricuspid stenosis (TS), which is much less prevalent than mitral stenosis (MS) in North America and Western Europe, is generally rheumatic in origin, and is more common in women than men (**Table 25-1**). It does not occur as an isolated lesion and is usually associated with MS. Hemodynamically significant TS occurs in 5–10% of patients with severe MS; rheumatic TS is commonly associated with some degree of tricuspid regurgitation (TR). Nonrheumatic causes of TS are rare.

PATHOPHYSIOLOGY

A diastolic pressure gradient between the right atrium (RA) and right ventricle (RV) defines TS. It is augmented when the transvalvular blood flow increases during inspiration and declines during expiration. A mean diastolic pressure gradient of 4 mmHg is usually sufficient to elevate the mean RA pressure to levels that result in systemic venous congestion. Unless sodium intake has been restricted and diuretics administered, this venous congestion is associated with hepatomegaly, ascites, and edema, sometimes severe. In patients with sinus rhythm, the RA a wave may be extremely tall and may even approach the level of the RV systolic pressure. The y descent is prolonged. The cardiac output (CO) at rest is usually depressed, and it fails to rise during exercise. The low CO is responsible for the normal or only slightly elevated left atrial (LA), pulmonary artery (PA), and RV systolic pressures despite the presence of MS. Thus, the presence of TS can mask the hemodynamic and clinical features of any associated MS.

SYMPTOMS

Because the development of MS generally precedes that of TS, many patients initially have symptoms of

pulmonary congestion and fatigue. Characteristically, patients with severe TS complain of relatively little dyspnea for the degree of hepatomegaly, ascites, and edema that they have. However, fatigue secondary to a low CO and discomfort due to refractory edema, ascites, and marked hepatomegaly are common in patients with advanced TS and/or TR. In some patients, TS may be suspected for the first time when symptoms of right-sided failure persist after an adequate mitral valvotomy.

PHYSICAL FINDINGS

Because TS usually occurs in the presence of other obvious valvular disease, the diagnosis may be missed unless it is considered. Severe TS is associated with marked hepatic congestion, often resulting in cirrhosis, jaundice, serious malnutrition, anasarca, and ascites. Congestive hepatomegaly and, in cases of severe tricuspid valve disease, splenomegaly are present. The jugular veins are distended, and in patients with sinus rhythm, there may be giant a waves. The v waves are less conspicuous, and because tricuspid obstruction impedes RA emptying during diastole, there is a slow y descent. In patients with sinus rhythm, there may be prominent presystolic pulsations of the enlarged liver as well.

On auscultation, an opening snap (OS) of the tricuspid valve may rarely be heard approximately 0.06 s after pulmonic valve closure. The diastolic murmur of TS has many of the qualities of the diastolic murmur of MS, and because TS almost always occurs in the presence of MS, it may be missed. However, the tricuspid murmur is generally heard best along the left lower sternal border and over the xiphoid process, and is most prominent during presystole in patients with sinus rhythm. The murmur of TS is augmented during inspiration, and it is reduced during expiration and particularly during the strain phase of the Valsalva maneuver, when tricuspid transvalvular flow is reduced.

TABLE 25-1

CAUSES OF TRICUSPID AND PULMONIC VALVE DISEASES	
VALVE LESION	ETIOLOGIES
Tricuspid stenosis	Rheumatic Congenital
Tricuspid regurgitation	Primary (organic) Rheumatic Endocarditis Myxomatous (TVP) Carcinoid Radiation Congenital (Ebstein's) Trauma Papillary muscle injury (post-MI) Secondary (functional) RV and tricuspid annular dilatation due to multiple causes of RV enlargement (e.g., long-standing pulmonary HTN, remodeling post-RVMI) Chronic RV apical pacing
Pulmonic stenosis	Congenital Carcinoid Tumor Endocarditis
Pulmonic regurgitation	Primary valve disease Congenital Postvalvotomy Endocarditis Carcinoid Annular enlargement Pulmonary hypertension Idiopathic dilation Marfan's syndrome

Abbreviations: HTN, hypertension; MI, myocardial infarction; RV, right ventricular; TVP, tricuspid valve prolapse.

LABORATORY EXAMINATION

The electrocardiogram (ECG) features of RA enlargement (see Fig. 11-8) include tall, peaked P waves in lead II, as well as prominent, upright P waves in lead V₁. The absence of ECG evidence of RV hypertrophy (RVH) in a patient with right-sided heart failure who is believed to have MS should suggest associated tricuspid valve disease. The chest x-ray in patients with combined TS and MS shows particular prominence of the RA and superior vena cava without much enlargement of the PA and with less evidence of pulmonary vascular congestion than occurs in patients with isolated MS. On echocardiographic examination, the tricuspid valve

is usually thickened and domes in diastole; the transvalvular gradient can be estimated by continuous wave Doppler echocardiography. Severe TS is characterized by a valve area $\leq 1\text{ cm}^2$ or pressure half-time of $\geq 190\text{ ms}$. The RA and inferior vena cava (IVC) are enlarged. Transthoracic echocardiography (TTE) provides additional information regarding the severity of any associated TR, mitral valve structure and function, left ventricle (LV) and RV size and function, and PA pressure. Cardiac catheterization is not routinely necessary for assessment of TS.

TREATMENT Tricuspid Stenosis

Patients with TS generally exhibit marked systemic venous congestion; salt restriction, bed rest, and diuretic therapy are required during the preoperative period. Such a preparatory period may diminish hepatic congestion and thereby improve hepatic function sufficiently so that the risks of operation, particularly bleeding, are diminished. Surgical relief of the TS should be carried out, preferably at the time of surgical mitral valvotomy or mitral valve replacement (MVR) for mitral valve disease, in patients with moderate or severe TS who have mean diastolic pressure gradients exceeding $\sim 4\text{ mmHg}$ and tricuspid orifice areas $< 1.5\text{--}2\text{ cm}^2$. TS is almost always accompanied by significant TR. Operative repair may permit substantial improvement of tricuspid valve function. If repair cannot be accomplished, the tricuspid valve may have to be replaced. Meta-analysis has shown no difference in overall survival between mechanical and tissue valve replacement. Mechanical valves in the tricuspid position are more prone to thromboembolic complications than in other positions. Percutaneous tricuspid balloon valvuloplasty for isolated severe TS without significant TR is very rarely performed.

TRICUSPID REGURGITATION

In at least 80% of cases, TR is secondary to marked dilation of the tricuspid annulus from RV enlargement due to PA hypertension (Table 25-1). Functional TR may complicate RV enlargement of any cause, however, including an inferior myocardial infarction (MI) that involves the RV. It is commonly seen in the late stages of heart failure due to rheumatic or congenital heart disease with severe PA hypertension (PA systolic pressure $> 55\text{ mmHg}$), as well as in ischemic and idiopathic dilated cardiomyopathies. It is reversible in part if PA hypertension can be relieved. Functional TR can also develop from chronic RV apical pacing. Rheumatic fever may produce primary (organic) TR, often associated with TS. Infarction of RV papillary muscles, tricuspid valve prolapse, carcinoid heart disease,

endomyocardial fibrosis, radiation, infective endocarditis, and leaflet trauma all may produce TR. Less commonly, TR results from congenitally deformed tricuspid valves, and it occurs with defects of the atrioventricular canal, as well as with Ebstein's malformation of the tricuspid valve (**Chap. 22**).

PATHOPHYSIOLOGY

The incompetent tricuspid valve allows blood to flow backward from the RV into the RA, the volume of which is dependent on the driving pressure (i.e., RV systolic pressure) and the size of the regurgitant orifice. The severity and physical signs of TR can vary as a function of PA systolic pressure (in the absence of RV outflow tract stenosis), the dimension of the tricuspid valve annulus, the respiratory cycle–dependent changes in RV preload, and RA compliance. RV filling is increased during inspiration. Forward CO is reduced and does not augment with exercise. Significant degrees of TR will lead to RA enlargement and elevation of the RA and jugular venous pressures with prominent c-v waves in the pulse tracings. Progressively severe TR can lead to “ventricularization” of the RA wave form (see **Fig. 9-1B**). Severe TR is also characterized by RV dilation (RV volume overload) and eventual systolic dysfunction, the rate of which can be accelerated by a concomitant pressure load from PA hypertension or by myocardial fibrosis from previous injury.

SYMPTOMS

Mild or moderate degrees of TR are usually well tolerated in the absence of other hemodynamic disturbances. Because TR most often coexists with left-sided valve lesions, LV dysfunction, and/or PA hypertension, symptoms related to these lesions may dominate the clinical picture. Fatigue and exertional dyspnea owing to reduced forward CO are early symptoms of isolated, severe TR. As the disease progresses and RV function declines, patients may report cervical pulsations, abdominal fullness/bloating, diminished appetite, and muscle wasting, although with progressive weight gain and painful swelling of the lower extremities.

PHYSICAL FINDINGS

The neck veins in patients with severe TR are distended with prominent c-v waves and rapid y descents (in the absence of TS). TR is more often diagnosed by examination of the neck veins than by auscultation of the heart sounds. Other findings may include marked hepatomegaly with systolic pulsations, ascites, pleural effusions, edema, and a positive hepatojugular reflex.

A prominent RV pulsation along the left parasternal region and a blowing holosystolic murmur along the lower left sternal margin, which may be intensified during inspiration (Carvallo's sign) and reduced during expiration or the strain phase of the Valsalva maneuver, are characteristic findings. The murmur of TR may sometimes be confused with that of MR unless attention is paid to its variation during the respiratory cycle and the extent of RV enlargement is appreciated. Atrial fibrillation (AF) is usually present in the chronic phase of the disease.

LABORATORY EXAMINATION

The ECG may show changes characteristic of the lesion responsible for the TR, e.g., an inferior Q-wave MI suggestive of a prior RV MI, RVH, or a bizarre right bundle branch block type pattern with preexcitation in patients with Ebstein's anomaly. ECG signs of RA enlargement may be present in patients with sinus rhythm; AF is frequently noted. The chest x-ray may show RA and RV enlargement, depending on the chronicity and severity of TR. TTE is usually definitive with demonstration of RA dilation and RV volume overload and prolapsing, flail, scarred, or displaced/tethered tricuspid leaflets; the diagnosis and assessment of TR can be made by color flow Doppler imaging (see **Fig. 12-8**). Severe TR is accompanied by hepatic vein systolic flow reversal. Continuous wave Doppler of the TR velocity profile is useful in estimating PA systolic pressure. Accurate assessment of TR severity, PA pressures, and RV size and systolic function with TTE can be quite challenging in many patients. Real-time three-dimensional echocardiography and cardiac magnetic resonance (CMR) imaging provide alternative imaging modalities, although they are not widely available. In patients with severe TR, the CO is usually markedly reduced, and the RA pressure pulse may exhibit no x descent during early systole but a prominent c-v wave with a rapid y descent. The mean RA and RV end-diastolic pressures are often elevated. Exercise testing can be used to assess functional capacity in patients with asymptomatic severe TR. The prognostic significance of exercise-induced changes in TR severity and RV function has not been well studied.

TREATMENT Tricuspid Regurgitation

Diuretics can be useful for patients with severe TR and signs of right heart failure (**Fig. 25-1**). An aldosterone antagonist may be particularly helpful because many patients have secondary hyperaldosteronism from marked hepatic congestion. Therapies to reduce elevated PA pressures and/or pulmonary vascular resistance, including

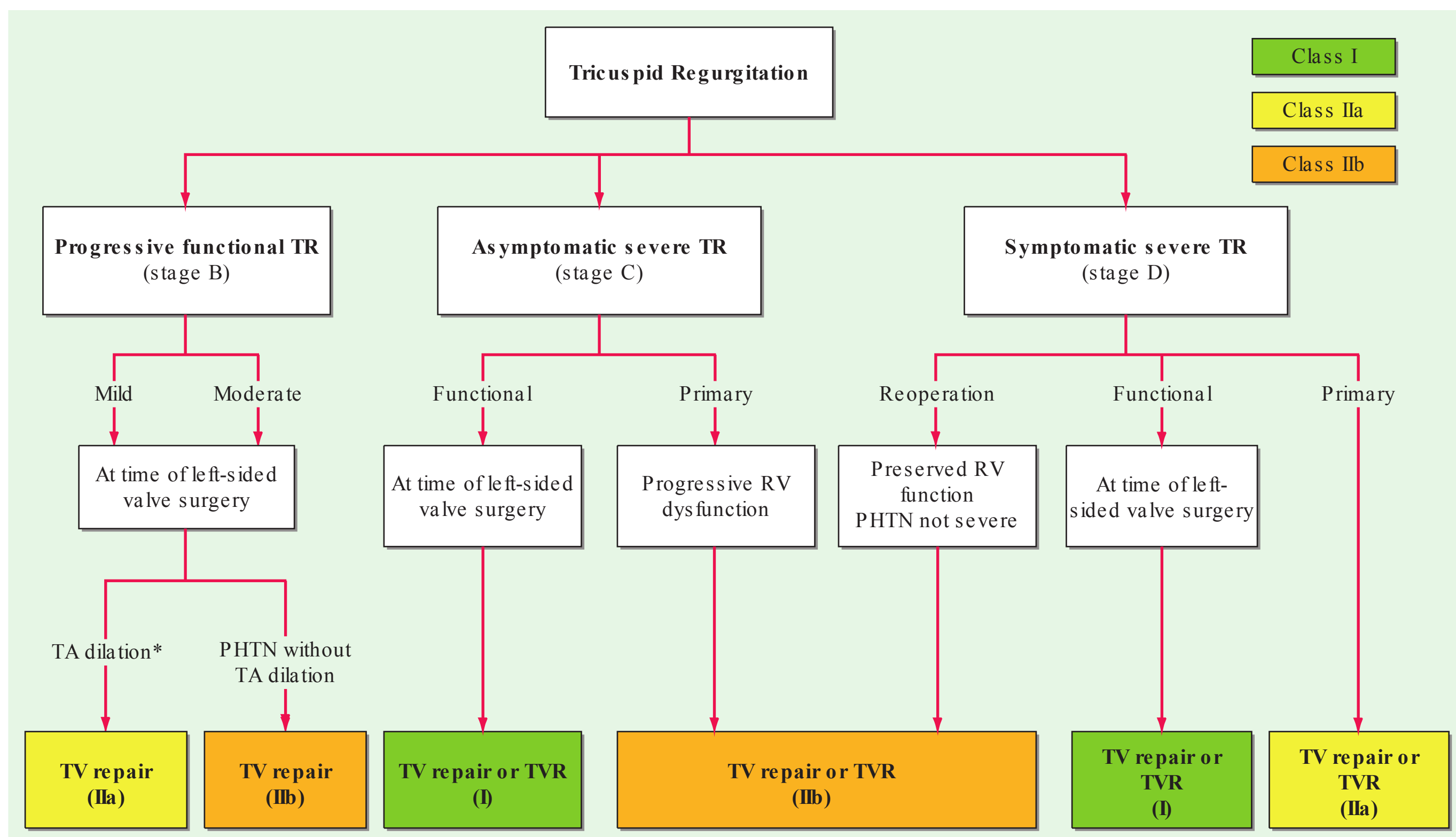


FIGURE 25-1

Management of tricuspid regurgitation. See legend for Fig. 23-2 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. PHTN, pulmonary hypertension; RV, right ventricular; TA, tricuspid annular; TIE, transthoracic

those targeted at left-sided heart disease, can also be considered for patients with PA hypertension and severe functional TR. Tricuspid valve surgery is recommended for patients with severe TR who are undergoing left-sided valve surgery and is also undertaken frequently for treatment of even moderate TR in patients undergoing left-sided valve surgery who have tricuspid annular dilation (>40 mm), a history of right heart failure, or PA hypertension. Operation most often comprises repair rather than replacement in these settings and has become routine in most major surgical centers. Surgery may also infrequently be required for treatment of severe, primary TR with right heart failure not responsive to standard medical therapy or because of progressively declining RV systolic function. Reported perioperative mortality rates for isolated tricuspid valve surgery (repair and replacement) are high (~ 8 – 9%) and likely are influenced by the hazards encountered during reoperation on patients who have undergone previous left-sided valve surgery and have reduced RV function. Indwelling pacemaker or defibrillator leads can also pose technical challenges.

echocardiogram; TR, tricuspid regurgitation; TV, tricuspid valve; TVR, tricuspid valve replacement. *TA dilation is defined by >40 mm on TIE (>21 mm/m²) or >70 mm on direct intraoperative measurement. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

PULMONIC STENOSIS

Pulmonic valve stenosis (PS) is essentially a congenital disorder (Table 25-1). With isolated PS, the valve is typically domed. Dysplastic pulmonic valves are seen as part of the Noonan's syndrome (**Chap. 47**), which maps to chromosome 12. Much less common etiologies include carcinoid and obstructing tumors or bulky vegetations. The pulmonic valve is only very rarely affected by the rheumatic process.

PATHOPHYSIOLOGY

PS is defined hemodynamically by a systolic pressure gradient between the RV and main PA. RV hypertrophy develops as a consequence of sustained obstruction to RV outflow, and systolic ejection is prolonged. Compared with the ability of the LV to compensate for the pressure overload imposed by aortic stenosis (AS), RV dysfunction from afterload mismatch occurs earlier in the course of PS and at lower peak systolic pressures, because the RV adapts less well to this type of hemodynamic burden.

With normal systolic function and CO, severe PS is defined by a peak systolic gradient across the pulmonic valve of >50 mmHg; moderate PS correlates with a peak gradient of 30–50 mmHg. PS rarely progresses in patients with peak gradients less than 30 mmHg, but may worsen in those with moderate disease due to valve thickening and calcification with age. The RA a wave elevates in relation to the higher pressures needed to fill a noncompliant, hypertrophied RV. A prominent RA v wave signifies functional TR from RV and annular dilation. The CO is maintained until late in the course of the disease.

SYMPTOMS

Patients with mild or even moderate PS are usually asymptomatic and first come to medical attention because of a heart murmur that leads to echocardiography. With severe PS, patients may report exertional dyspnea or early-onset fatigue. Anginal chest pain from RV oxygen supply-demand mismatch and syncope may occur with very severe forms of obstruction, particularly in the presence of a destabilizing trigger such as atrial fibrillation, fever, infection, or anemia.

PHYSICAL FINDINGS

The murmur of mild or moderate PS is mid-systolic in timing, crescendo-decrescendo in configuration, heard best in the left second interspace, and usually introduced by an ejection sound (click) in younger adults whose valves are still pliable. The ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. This phenomenon reflects premature opening of the pulmonic valve by the elevated RV end-diastolic (postatrial a wave) pressure. The systolic murmur increases in intensity during inspiration. With progressively severe PS, the ejection sound moves closer to the first heart sound and eventually becomes inaudible. A right-sided fourth heart sound may emerge. The systolic murmur peaks later and may persist through the aortic component of the second heart sound (A_2). Pulmonic valve closure is delayed, and the pulmonic component of the second heart sound (P_2) is reduced or absent. A prominent a wave, indicative of the higher atrial pressure necessary to fill the noncompliant RV, may be seen in the jugular venous pulse. A parasternal or RV lift can be felt with significant pressure overload. Signs of right heart failure, such as hepatomegaly, ascites, and edema, are uncommon but may appear very late in the disease.

LABORATORY EXAMINATION

The ECG will show right axis deviation, RVH, and RA enlargement in adult patients with severe PS. Chest x-ray findings include poststenotic dilation of the main

PA in the frontal plane projection and filling of the retrosternal airspace due to RV enlargement on the lateral film. In some patients with RVH, the cardiac apex appears to be lifted off the left hemidiaphragm. The RA may also be enlarged. TTE allows definitive diagnosis and characterization in most cases, with depiction of the valve and assessment of the gradient, RV function, PA pressures (which should be low), and any associated cardiac lesions. TEE may be useful in some patients for improved delineation of the RV outflow tract (RVOT) and assessment of infundibular hypertrophy. Cardiac catheterization is not usually necessary, but if performed, pressures should be obtained from just below and above the pulmonic valve with attention to the possibility that a dynamic component to the gradient may exist. The correlation between Doppler assessment of peak instantaneous gradient and catheterization-measured peak-to-peak gradient is weak. The latter may correlate better with the Doppler mean gradient.

TREATMENT Pulmonic Stenosis

Diuretics can be used to treat symptoms and signs of right heart failure. Provided there is less than moderate pulmonic regurgitation, pulmonic balloon valvotomy is recommended for symptomatic patients with a domed valve and a peak gradient >50 mmHg (or mean gradient >30 mmHg) and for asymptomatic patients with a peak gradient >60 mmHg (or mean gradient >40 mmHg). Surgery may be required when the valve is dysplastic (as seen in patients with Noonan's syndrome and other disorders). A multidisciplinary heart team is best positioned to make treatment decisions of this nature.

PULMONIC REGURGITATION

Pulmonic regurgitation (PR) may develop as a consequence of primary valve pathology, annular enlargement, or their combination; after surgical treatment of RVOT obstruction in children with such disorders as tetralogy of Fallot; or after pulmonic balloon valvotomy (Table 25-1). Carcinoid usually causes mixed pulmonic valve disease with PR and PS. Long-standing severe PA hypertension from any cause can result in dilation of the pulmonic valve ring and PR.

PATHOPHYSIOLOGY

Severe PR results in RV chamber enlargement and eccentric hypertrophy. As is the case for aortic regurgitation (AR), PR is a state of increased preload and afterload. The reverse pressure gradient from the PA to the RV, which drives the PR, progressively decreases throughout diastole and accounts for the decrescendo

nature of the diastolic murmur. As RV diastolic pressure increases, the murmur becomes shorter in duration. The forward CO is preserved during the early stages of the disease, but may not increase normally with exercise and declines over time. A reduction in RV ejection fraction may be an early indicator of hemodynamic compromise. In advanced stages, there is significant enlargement of the RV and RA with marked elevation of the jugular venous pressure.

SYMPTOMS

Mild or moderate degrees of PR do not, by themselves, result in symptoms. Other problems, such as PA hypertension, may dominate the clinical picture. With progressively severe PR and RV dysfunction, fatigue, exertional dyspnea, abdominal fullness/bloating, and lower extremity swelling may be reported.

PHYSICAL FINDINGS

The physical examination hallmark of PR is a high-pitched, decrescendo diastolic murmur (Graham Steell murmur) heard along the left sternal border that can be difficult to distinguish from the more frequently appreciated murmur of aortic regurgitation. The Graham Steell murmur may become louder with inspiration and is usually associated with a loud and sometimes palpable P_2 and an RV lift, as would be expected in patients with significant PA hypertension of any cause. Survivors of childhood surgery for tetralogy of Fallot or PS/pulmonary atresia may have an RV-PA conduit that is freely regurgitant because it does not contain a valve. PA pressures in these individuals are not elevated and the diastolic murmur can be misleadingly low pitched

and of short duration despite significant degrees of PR and RV volume overload.

LABORATORY EXAMINATION

Depending on both the etiology and severity of PR, the ECG may show findings of RVH and RA enlargement. On chest x-ray, the RV and RA may be enlarged. Pulmonic valve morphology and function can be assessed with transthoracic Doppler echocardiography. PA pressures can be estimated from the tricuspid valve systolic jet velocity. CMR provides greater anatomic detail, particularly in patients with repaired congenital heart disease, and more precise assessment of RV volumes. Cardiac catheterization is not routinely necessary but would be performed as part of a planned transcatheter procedure.

TREATMENT Pulmonic Regurgitation

In patients with functional PR due to PA hypertension and annular dilation, efforts to reduce PA vascular resistance and pressure should be optimized. Such efforts may include pharmacologic/vasodilator and/or surgical/interventional strategies, depending on the cause of the PA hypertension. Diuretics can be used to treat the manifestations of right heart failure. Surgical valve replacement for primary, severe, pulmonic valve disease, such as carcinoid or endocarditis, is rarely undertaken. Transcatheter pulmonic valve replacement has been successfully performed in many patients with severe PR after childhood repair of tetralogy of Fallot or pulmonic valve stenosis or atresia. This procedure was introduced clinically prior to transcatheter aortic valve replacement.

CHAPTER 26

MULTIPLE AND MIXED VALVULAR HEART DISEASE



Patrick T. O’Gara ■ Joseph Loscalzo

Many acquired and congenital cardiac lesions may result in stenosis and/or regurgitation of one or more heart valves. For example, rheumatic heart disease can involve the mitral (mitral stenosis [MS], mitral regurgitation [MR], or MS and MR), aortic (aortic stenosis [AS], aortic regurgitation [AR], or AS and AR), and/or tricuspid (tricuspid stenosis [TS], tricuspid regurgitation [TR], or TS and TR) valve, alone or in combination. The common association of functional TR with significant mitral valve disease is discussed in **Chap. 25**. Severe mitral annular calcification can result in regurgitation (due to decreased annular shortening during systole) and mild stenosis (caused by extension of the calcification onto the leaflets resulting in restricted valve opening). Patients with severe AS may develop functional MR that may not improve after isolated aortic valve replacement (AVR). Chordal rupture has been described infrequently in patients with severe AS. Aortic valve infective endocarditis may secondarily involve the mitral apparatus either by abscess formation and contiguous spread via the intervalvular fibrosa or by “drop metastases” from the aortic leaflets onto the anterior leaflet of the mitral valve. Mediastinal radiation may result in aortic, mitral, and even tricuspid valve disease, most often with mixed stenosis and regurgitation. Carcinoid heart disease may cause mixed lesions of either or both the tricuspid and pulmonic valves. Ergotamines, and the previously used combination of fenfluramine and phentermine, can rarely result in mixed lesions of the aortic and/or mitral valve. Patients with Marfan’s syndrome may have both AR from aortic root dilation and MR due to mitral valve prolapse (MVP). Myxomatous degeneration causing prolapse of multiple valves (mitral, aortic, tricuspid) can also occur in the absence of an identifiable connective tissue disorder. Bicuspid aortic or pulmonic valve disease can result in mixed stenosis and regurgitation.

PATHOPHYSIOLOGY

In patients with multivalvular heart disease, the pathophysiologic derangements associated with the more proximal valve disease can mask the full expression of the attributes of the more distal valve lesion. For example, in patients with rheumatic mitral and aortic valve disease, the reduction in cardiac output (CO) imposed by the mitral valve disease will decrease the magnitude of the hemodynamic derangements related to the severity of the aortic valve lesion (stenotic, regurgitant, or both). Alternatively, the development of atrial fibrillation (AF) during the course of MS can lead to sudden worsening in a patient whose aortic valve disease was not previously felt to be significant. The development of reactive pulmonary vascular disease, sometimes referred to as a “secondary obstructive lesion in series,” can impose an additional challenge in these settings. As CO falls with progressive tricuspid valve disease, the severity of any associated mitral or aortic disease can be underestimated.

One of the most common examples of multivalve disease is that of functional TR in the setting of significant mitral valve disease. Functional TR occurs as a consequence of right ventricular and annular dilation; pulmonary artery (PA) hypertension is often present. The tricuspid leaflets are morphologically normal. Progressive degrees of TR lead to right ventricular volume overload and continued chamber and annular dilation. The TR is usually central in origin; reflux into the right atrium (RA) is expressed as large, systolic c-v waves in the RA pressure pulse. The height of the c-v wave is dependent on RA compliance and the volume of regurgitant flow. The RA wave form may become “ventricularized” in advanced stages of chronic, severe TR with PA hypertension. CO falls and the severity of the associated mitral valve disease may become more difficult to appreciate. Primary rheumatic tricuspid valve disease

may occur with rheumatic mitral disease and cause hemodynamic changes reflective of TR, TS, or their combination. With TS, the y descent in the RA pressure pulse is prolonged.

Another example of rheumatic, multivalve disease involves the combination of mitral and aortic valve pathology, frequently characterized by MS and AR. In isolated MS, left ventricular (LV) preload and diastolic pressure are reduced as a function of the severity of inflow obstruction. With concomitant AR, however, LV filling is enhanced and diastolic pressure may rise depending on the compliance characteristics of the chamber. Because the CO falls with progressive degrees of MS, transaortic valve flows will decline, masking the potential severity of the aortic valve lesion (AR, AS, or its combination). As noted above, onset of AF in such patients can be especially deleterious.

Functional MR may complicate the course of some patients with severe AS. The mitral valve leaflets and chordae tendineae are usually normal. Incompetence is related to changes in LV geometry (remodeling) and abnormal systolic tethering of the leaflets in the context of markedly elevated LV systolic pressures. Relief of the excess afterload with surgical or transcatheter AVR often, but not always, results in reduction or elimination of the MR. Persistence of significant MR following AVR is associated with impaired functional outcomes and reduced survival. Identification of patients who would benefit from concomitant treatment of their functional MR at time of AVR is quite challenging. Most surgeons advocate for repair of moderate-to-severe or severe functional MR at time of surgical AVR.

In patients with mixed AS and AR, assessment of valve stenosis can be influenced by the magnitude of the regurgitant valve flow. Because transvalvular systolic flow velocities are augmented in patients with AR and preserved LV systolic function, the LV-aortic Doppler-derived pressure gradient and the intensity of the systolic murmur will be elevated to values higher than expected for the true systolic valve orifice size as delineated by planimetry. Uncorrected, the Gorlin formula, which relies on forward CO (systolic transvalvular flow) and the mean pressure gradient for calculation of valve area, is not accurate in the setting of mixed aortic valve disease. Similar considerations apply to patients with mixed mitral valve disease. The peak mitral valve Doppler E wave velocity (v_0) is increased in the setting of severe MR because of enhanced early diastolic flow and may not accurately reflect the contribution to left atrial (LA) hypertension from any associated MS. When either AR or MR is the dominant lesion in patients with mixed aortic or mitral valve disease, respectively, the LV is dilated. When AS or MS predominates, LV chamber size will be normal or small. It can sometimes be

difficult to ascertain whether stenosis or regurgitation is the dominant lesion in patients with mixed valve disease, although an integrated clinical and noninvasive assessment can usually provide clarification for purposes of patient management and follow-up.

Patients with significant AS, a nondilated LV chamber, and concentric hypertrophy will poorly tolerate the abrupt development of aortic regurgitation, as may occur, for example, with infective endocarditis or after surgical or transcatheter AVR complicated by paravalvular leakage. The noncompliant LV is not prepared to accommodate the sudden volume load, and as a result, LV diastolic pressure rises rapidly and severe heart failure develops. Indeed, paravalvular regurgitation is a significant risk factor for short- to intermediate-term death following transcatheter AVR. Conditions in which the LV may not be able to dilate in response to chronic AR (or MR) include radiation heart disease and, in some patients, the cardiomyopathy associated with obesity and diabetes. Noncompliant ventricles of small chamber size predispose to earlier onset diastolic dysfunction and heart failure in response to any further perturbation in valve function.

SYMPTOMS

Compared with patients with isolated, single-lesion valve disease, patients with multiple or mixed valve disease may develop symptoms at a relatively earlier stage in the natural history of their disease. Symptoms such as exertional dyspnea and fatigue are usually related to elevated filling pressures, reduced CO, or their combination. Palpitations may signify AF and identify mitral valve disease as an important component of the clinical presentation, even when not previously suspected. Chest pain compatible with angina could reflect left or right ventricular oxygen supply/demand mismatch on a substrate of hypertrophy and pressure/volume overload with or without superimposed coronary artery disease. Symptoms related to right heart failure (abdominal fullness/bloating, edema) are late manifestations of advanced disease.

PHYSICAL FINDINGS

Mixed disease of a single valve is most often manifested by systolic and diastolic murmurs, each with the attributes expected for the valve in question. Thus, patients with AS and AR will have characteristic mid-systolic, crescendo-decrescendo and blowing, decrescendo diastolic murmurs at the base of the heart in the second right interspace and along the left sternal edge, respectively. Many patients with significant AR have mid-systolic outflow murmurs even in the absence of valve

sclerosis/stenosis, and other findings of AS must be sought. The separate murmurs of AS and AR can occasionally be difficult to distinguish from the continuous murmurs associated with either a patent ductus arteriosus (PDA) or ruptured sinus of Valsalva aneurysm. With mixed aortic valve disease, the systolic murmur should end before, and not envelope or extend through, the second heart sound (S_2). The murmur associated with a PDA is heard best to the left of the upper sternum. The continuous murmur heard with a ruptured sinus of Valsalva aneurysm is often first appreciated after an episode of acute chest pain. An early ejection click, which usually defines bicuspid aortic valve disease in young adults, is often not present in patients with congenital, mixed AS and AR. As noted above, both the intensity and duration of these separate murmurs can be influenced by a reduction in CO and transvalvular flow due to coexistent mitral valve disease. In patients with isolated MS and MR, expected findings would include a blowing, holosystolic murmur and a mid-diastolic rumble (with or without an opening snap) best heard at the cardiac apex. An irregularly irregular heart rhythm in such patients would likely signify AF. Findings with TS and TR would mimic those of left-sided MS and MR, save for the expected changes in the murmurs with respiration. The murmurs of pulmonic stenosis and regurgitation behave in a fashion directionally similar to AS and AR; dynamic changes during respiration should be noted. **Specific attributes of these cardiac murmurs are reviewed in Chap. 25.**

LABORATORY EXAMINATION

The electrocardiogram (ECG) may show evidence of ventricular hypertrophy and/or atrial enlargement. ECG signs indicative of right-sided cardiac abnormalities in patients with left-sided valve lesions should prompt additional assessment for PA hypertension and/or right-sided valve disease. The presence of AF in patients with aortic valve disease may be a clue to the presence of previously unsuspected mitral valve disease in the appropriate context. The chest x-ray can be reviewed for evidence of cardiac chamber enlargement, valve and/or annular calcification, and any abnormalities in the appearance of the pulmonary vasculature. The latter could include enlargement of the main and proximal pulmonary arteries with PA hypertension and pulmonary venous redistribution/engorgement or Kerley B lines with increasing degrees of LA hypertension. An enlarged azygos vein in the frontal projection indicates RA hypertension. Roentgenographic findings not expected based on a single or mixed valve lesion may reflect other valve disease.

Transthoracic echocardiography (TTE) is the most commonly used imaging modality for the diagnosis

and characterization of multiple and/or mixed valvular heart disease and may often demonstrate findings not clinically suspected. Transesophageal echocardiography (TEE) may sometimes be required for more accurate assessment of valve anatomy (specifically, the mitral valve) and when infective endocarditis (IE) is considered responsible for the clinical presentation. TTE findings of particular interest include those related to valve morphology and function, calcification, chamber size, ventricular wall thickness, estimated PA systolic pressure, and the dimensions of the great vessels, including the root and ascending aorta, PA, and inferior vena cava. Exercise testing (with or without echocardiography) can be useful when the degree of functional limitation reported by the patient is not adequately explained by the findings on TTE performed at rest. An integrated assessment of the clinical and TTE findings is needed to help determine the dominant valve lesion(s) and establish an appropriate plan for treatment and follow-up. Natural history is usually influenced to a relatively greater degree by the dominant lesion. Exercise testing (with or without echocardiography) can Cardiac magnetic resonance (CMR) can be used to provide additional anatomic and physiologic information when echocardiography proves suboptimal, but is less well suited to the evaluation of valve morphology. Cardiac computed tomography (CT) has been used to assess intracardiac structures in patients with complicated IE. Coronary CT angiography provides a noninvasive alternative for the assessment of coronary artery anatomy prior to surgery.

Invasive hemodynamic evaluation with right and left heart catheterization may be required to characterize more completely the individual contributions of each lesion in patients with either multiple or mixed valvular heart disease. Measurement of PA pressures and calculation of pulmonary vascular resistance (PVR) can help inform clinical decision-making in certain patient subsets, such as those with advanced mitral and tricuspid valve disease. Attention to the accurate assessment of CO is essential. Coronary angiography (if indicated) can be performed as part of the procedure. Contrast ventriculography and great vessel angiography are performed infrequently.

TREATMENT Multiple and Mixed Valve Disease

Management of patients with multiple or mixed valve disease can be challenging. As noted above, it is helpful to determine the dominant valve lesion and proceed according to the treatment and follow-up recommendations for it (**Chaps. 23 to 25**), being mindful of deviations from the expected course because of problems related to another valve disorder. For example, AF that emerges in the course of moderate mitral

valve disease may precipitate heart failure in patients with concomitant, severe aortic valve disease.

Medical therapies are limited and include diuretics when indicated for relief of congestion and vitamin K antagonists for anticoagulation to prevent stroke and thromboembolism in patients with AF. The novel oral anticoagulants are not approved for use in the setting of significant valvular heart disease. Blood pressure-lowering medications may be needed to treat systemic hypertension, which may aggravate left-sided regurgitant valve lesions, but should be initiated and titrated carefully. Pulmonary vasodilators to lower PVR are not generally effective in this context.

There is a paucity of evidence to inform practice guidelines for surgical and/or transcatheter valve intervention in patients with multiple or mixed valve disease. When there is a clear, dominant lesion, as for example in a patient with severe AS and mild AR, indications for intervention are straightforward and follow those recommended for patients with AS (**Chap. 23**). In other patients, however, there is less clarity, and decisions regarding intervention should be based on several considerations, including those related to lesion severity, ventricular remodeling, functional capacity, and PA pressures. In this regard, it is important to realize that patients with multiple and/or mixed valve disease may develop limiting symptoms or signs of physiologic impairment even with moderate valve lesions.

Concomitant aortic and mitral valve replacement surgery is associated with a significantly higher perioperative mortality risk than replacement of either valve alone (see **Tables 23-2 and 24-2**), and operation should be carefully considered. Double valve replacement surgery is usually performed for treatment of severe (unrepairable) valve disease at both locations and for the combination of severe disease at

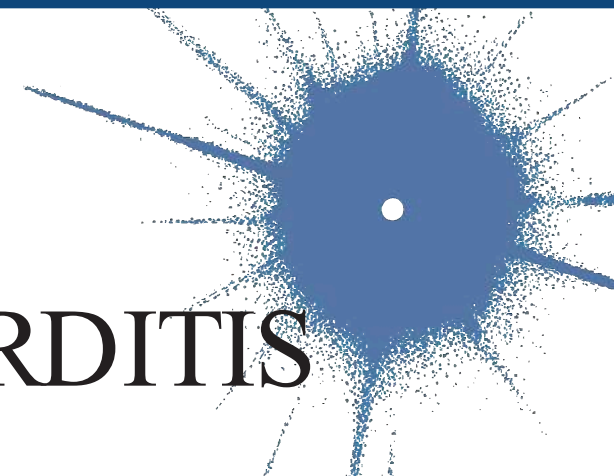
one location with moderate disease at the other, so as to avoid the hazards of reoperation in the intermediate to late term for progressive disease of the unoperated valve. In addition, the presence of a prosthesis in the aortic position significantly restricts surgical exposure of the native mitral valve. The need for double valve replacement may also impact the decision regarding the type of prosthesis (i.e., mechanical vs tissue).

Tricuspid valve repair for moderate or severe functional TR at the time of left-sided valve surgery is now commonplace, particularly if there is dilation of the tricuspid annulus (>40 mm). The addition of tricuspid valve repair, consisting usually of insertion of an annuloplasty ring, adds little time or complexity to the procedure and is well tolerated. Reoperation for repair (or replacement) of progressive TR years after initial surgery for left-sided valve disease, on the other hand, is associated with a relatively high perioperative mortality risk. Repair of moderate or severe functional MR at time of AVR for AS can usually be undertaken with acceptable risk for perioperative death or major complication.

The presence of moderate or severe MR in patients with rheumatic MS is a contraindication to percutaneous mitral balloon valvotomy (PMBV). Likewise, the presence of significant AR in patients with AS disqualifies them from percutaneous aortic balloon valvotomy (PABV). The presence of severe, coexistent AR was an exclusion criterion for enrollment in the initial PARTNER trials of transcatheter AVR (TAVR) in prohibitive- and high-surgical-risk patients with severe, calcific AS. Transcatheter management of both severe AS (with TAVR) and functional MR (with deployment of a MitralClip) has been reported. Further advances in transcatheter treatments for multiple and mixed valve disease are anticipated.

CHAPTER 27

CARDIOMYOPATHY AND MYOCARDITIS



Neal K. Lakdawala ■ Lynne Warner Stevenson ■ Joseph Loscalzo

DEFINITION AND CLASSIFICATION

Cardiomyopathy is disease of the heart muscle. It is estimated that cardiomyopathy accounts for 5–10% of the heart failure in the 5–6 million patients carrying that diagnosis in the United States. The term is intended to exclude cardiac dysfunction that results from other structural heart disease, such as coronary artery disease, primary valve disease, or severe hypertension; however, in general usage, the phrase ischemic cardiomyopathy is sometimes applied to describe diffuse dysfunction attributed to multivessel coronary artery disease, and nonischemic cardiomyopathy to describe cardiomyopathy from other causes. As of 2006, cardiomyopathies are defined as “a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic.”¹

The traditional classification of cardiomyopathies into a triad of dilated, restrictive, and hypertrophic was based initially on autopsy specimens and later on echocardiographic findings. Dilated and hypertrophic cardiomyopathies can be distinguished on the basis of left ventricular wall thickness and cavity dimension; however, restrictive cardiomyopathy can have variably increased wall thickness and chamber dimensions that range from reduced to slightly increased, with prominent atrial enlargement. Restrictive cardiomyopathy is now defined more on the basis of abnormal diastolic function, which is also present but initially less prominent in dilated and hypertrophic cardiomyopathy. Restrictive cardiomyopathy can overlap in presentation, gross morphology, and etiology with both hypertrophic and dilated cardiomyopathies (**Table 27-1**).

Expanding information renders this classification triad based on phenotype increasingly inadequate to define disease or therapy. Identification of more genetic determinants of cardiomyopathy has suggested a four-way classification scheme of etiology as primary (affecting primarily the heart) and secondary to other systemic disease. The primary causes are then divided into genetic, mixed genetic and acquired, and acquired; however, genetic information is often unavailable at the time of initial presentation, the phenotypic expression of a given mutation varies widely, and genetic predisposition influences the clinical phenotype of acquired cardiomyopathies, as well. Although the proposed genetic classification does not yet guide many current clinical strategies, it will likely become increasingly relevant as classification of disease moves beyond individual organ pathology to more integrated systems approaches.

GENERAL PRESENTATION

For all cardiomyopathies, the early symptoms often relate to exertional intolerance with breathlessness or fatigue, usually from inadequate cardiac reserve during exercise. These symptoms may initially go unnoticed or be attributed to other causes, commonly lung disease or age-dependent exercise limitation. As fluid retention leads to elevation of resting filling pressures, shortness of breath may occur during routine daily activity such as dressing and may manifest as dyspnea or cough when lying down at night. Although often considered the hallmark of congestion, peripheral edema may be absent despite severe fluid retention, particularly in younger patients in whom ascites and abdominal discomfort may dominate. The nonspecific term congestive heart failure describes only the resulting syndrome of fluid retention, which is common to all three types of cardiomyopathy and also to cardiac structural diseases associated with elevated filling pressures. All three

¹From BJ Maron et al: Circulation 113:1807, 2006.

TABLE 27-1

	DILATED	RESTRICTIVE	HYPERTROPHIC
Ejection fraction (normal >55%)	Usually <30% when symptoms severe	25–50%	>60%
Left ventricular diastolic dimension (normal <55 mm)	≥60 mm	<60 mm (may be decreased)	Often decreased
Left ventricular wall thickness	Normal or decreased	Normal or increased	Markedly increased
Atrial size	Increased, may also be primarily affected	Increased; may be massive	Increased; related to elevated filling pressures
Valvular regurgitation	Related to annular dilation; mitral appears earlier during decompensation; tricuspid regurgitation with right ventricular dysfunction	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction; mitral regurgitation
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early, may have dominant right-sided symptoms	Exertional intolerance; may have chest pain
Congestive symptoms ^a	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion at rest may develop late
Arrhythmias	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families. Atrial fibrillation.	Ventricular uncommon except in sarcoidosis, conduction block in sarcoidosis and amyloidosis. Atrial fibrillation.	Ventricular tachyarrhythmias; atrial fibrillation

^aLeft-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea. Right-sided symptoms of systemic venous congestion: hepatic and abdominal distention, discomfort on bending, peripheral edema.

types of cardiomyopathy can be associated with atrioventricular valve regurgitation, typical and atypical chest pain, atrial and ventricular tachyarrhythmias, and embolic events (Table 27-1). Initial evaluation begins with a detailed clinical history and examination, looking for clues to cardiac, extracardiac, and familial disease (Table 27-2).

GENETIC ETIOLOGIES OF CARDIOMYOPATHY



Estimates for the prevalence of genetic etiology for cardiomyopathy continue to rise, with increasing attention paid to the family history and the availability of genetic testing. Well-recognized in hypertrophic cardiomyopathy, heritability is also present in at least 30% of dilated cardiomyopathy without other clear etiology. Careful family history should elicit not only known cardiomyopathy and heart failure, but also family members who have had sudden death, often incorrectly attributed to “a massive heart attack,” who have had atrial fibrillation or pacemaker implantation by middle age, or who have muscular dystrophy.

Most familial cardiomyopathies are inherited in an autosomal dominant pattern, with occasional autosomal recessive and X-linked inheritance (Table 27-3). Missense mutations with amino acid substitutions are the most common in cardiomyopathy. Expressed mutant proteins may interfere with function of the normal allele through a dominant negative mechanism. Mutations introducing a premature stop codon (nonsense) or shift in the reading frame (frameshift) may create a truncated or unstable protein the lack of which causes cardiomyopathy (haploinsufficiency). Deletions or duplications of an entire exon or gene are uncommon causes of cardiomyopathy, except for the dystrophinopathies.

Many different genes have been implicated in human cardiomyopathy (locus heterogeneity), and many mutations within those genes have been associated with disease (allelic heterogeneity). Although most identified mutations are “private” to individual families, several specific mutations are found repeatedly, either due to a founder effect or recurrent mutations at a common residue.

Genetic cardiomyopathy is characterized by age dependence and incomplete penetrance. The defining phenotype of cardiomyopathy is rarely present at birth and, in some individuals, may never manifest. Related individuals

TABLE 27-2

INITIAL EVALUATION OF CARDIOMYOPATHY					
Clinical Evaluation					
Thorough history and physical examination to identify cardiac and noncardiac disorders ^a					
Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders, tachyarrhythmias, and sudden death					
History of alcohol, illicit drugs, chemotherapy or radiation therapy ^a					
Assessment of ability to perform routine and desired activities ^a					
Assessment of volume status, orthostatic blood pressure, body mass index ^a					
Laboratory Evaluation					
Electrocardiogram ^a					
Chest radiograph ^a					
Two-dimensional and Doppler echocardiogram ^a					
Magnetic resonance imaging for evidence of myocardial inflammation and fibrosis					
Chemistry:					
Serum sodium, ^a potassium, ^a calcium, ^a magnesium ^a					
Fasting glucose (glycohemoglobin in diabetes mellitus)					
Creatinine, ^a blood urea nitrogen ^a					
Albumin, ^a total protein, ^a liver function tests ^a					
Lipid profile					
Thyroid-stimulating hormone ^a					
Serum iron, transferrin saturation					
Urinalysis					
Creatine kinase isoforms					
Cardiac troponin levels					
Hematology:					
Hemoglobin/hematocrit ^a					
White blood cell count with differential, ^a including eosinophils					
Erythrocyte sedimentation rate					
Initial Evaluation When Specific Diagnoses Are Suspected					
Titers for infection in the setting of clinical suspicion:					
Acute viral (coxsackie, echovirus, influenza)					
Human immunodeficiency virus					
Chagas' (Trypanosoma cruzi), Lyme (Borrelia burgdorferi), toxoplasmosis					
Catheterization with coronary angiography in patients with angina who are candidates for intervention ^a					
Serologies for active rheumatologic disease					
Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications					
Screening for sleep-disordered breathing					

^aLevel I recommendations from ACC/AHA Practice Guidelines for Chronic Heart Failure in the Adult.

TABLE 27-3

SELECTED GENETIC DEFECTS ASSOCIATED WITH CARDIOMYOPATHY					
	GENE PRODUCT	INHERITANCE	CARDIAC PHENOTYPE	ISOLATED CARDIAC PHENOTYPE	EXTRACARDIAC MANIFESTATIONS
Sarcomere	MYH7 (β myosin heavy chain)	AD	HCM, DCM, LVNC	Yes	Skeletal myopathy
	MYBPC3 (myosin binding protein C)	AD	HCM	Yes	
	TNNT2 (cardiac troponin T)	AD	HCM, DCM, LVNC	Yes	
	TNNI3 (cardiac troponin I)	AD, AR	HCM, DCM, RCM	Yes	
	TIN (Titin)	AD	DCM	Yes	
	TPM1 (α-tropomyosin)	AD	HCM, DCM	Yes	

TABLE 27-3

SELECTED GENETIC DEFECTS ASSOCIATED WITH CARDIOMYOPATHY (CONTINUED)					
	GENE PRODUCT	INHERITANCE	CARDIAC PHENOTYPE	ISOLATED CARDIAC PHENOTYPE	EXTRACARDIAC MANIFESTATIONS
	TNNC1 (cardiac troponin C)	AD	DCM	Yes	Skeletal myopathy
	ACTC (α -actin)	AD	HCM, DCM, (LVNC)	Yes	
	MYL2 (myosin regulatory light chain)	AD	HCM	Yes	
	MYL3 (myosin essential light chain)	AD	HCM	Yes	
Z-disk and Cytoskeleton	DES (Desmin)	AD	DCM, RCM	Yes	Skeletal myopathy
	LDB3 (Cypher-ZASP)	AD	DCM, LVNC	Yes	Skeletal myopathy
	MYOZ2 (Myozenin)	AD	HCM	Yes	
	TCAP (Telethonin)	AD	DCM, HCM	Yes	
	ANKRD1 (CARP)	AD	HCM, (DCM)	Yes	
	CSRP3 (MLP)	AD	DCM, (HCM)	Yes	
	ACTN2 (α -actinin-2)	AD	DCM	Yes	
	CRYAB (α B-crystallin)	AD	DCM	Yes	
Nuclear Membrane	LMNA (Lamin A/C)	AD, AR	CDDC	Yes	Skeletal myopathy
	EMD (Emerin)	X-linked	CDDC	No	Skeletal myopathy, contractures
Excitation-Contraction Coupling	PLN (Phospholamban)	AD	DCM	Yes	Note other mutations associated with Brugada syndrome
	SCN5A (NAV 1.5)	AD	CDDC	Yes	
	RYR2 (cardiac ryanodine receptor)	AD	ARVC	Yes	
	CASQ2 (calsequestrin 2)	AR	ARVC	Yes	
Cellular Metabolism	PRKAG2 (γ -subunit of AMP kinase)	AD	HCM+	Yes	Danon's disease: skeletal myopathy, cognitive impairment Barth's syndrome: skeletal myopathy, cognitive impairment, neutropenia Friedreich's ataxia: ataxia, diabetes mellitus type 2 Fabry's disease: renal failure, angiokeratomas and painful neuropathy
	LAMP2 (lysosomal associated membrane protein)	X-linked	HCM+	No ^a	
	TAZ (Tafazzin)	X-linked	DCM, LVNC	No	
	FXN (Frataxin)	AR	HCM	No	
	TMEM43 (transmembrane protein 43)	AD	ARVC	Yes	
	GLA (α -galactosidase-A)	X-linked	HCM+	Yes	
Mitochondria	Mitochondrial DNA	Maternal transmission	DCM, HCM	No	MELAS, MERRE, Kearns-Sayre syndrome, ocular myopathy

(continue)

TABLE 27-3

SELECTED GENETIC DEFECTS ASSOCIATED WITH CARDIOMYOPATHY (CONTINUED)					
	GENE PRODUCT	INHERITANCE	CARDIAC PHENOTYPE	ISOLATED CARDIAC PHENOTYPE	EXTRACARDIAC MANIFESTATIONS
Sarcolemmal Membrane	DMD (Dystrophin)	X-linked	DCM	No ^a	Duchenne’s and Becker’s muscular dystrophy
	DMPK(dystrophica myotonica protein kinase)	AD	DCM	No	Myotonic dystrophy type 1
	SGCD (δ-sarcoglycan)	AD	DCM	Yes	
Desmosome	DSP (Desmoplakin) JUP (Plakoglobin)	AD, AR	ARVC	Yes	Carvajal syndrome (AR), Naxos syndrome (AR), “woolly hair” and hyperkeratosis of palms and soles
	DSG2 (Desmoglein 2) DSC2 (Desmocollin 2) PKP2 (Plakophilin 2)	AD	ARVC	Yes	
Other Examples	RBM20 (RNA binding motif 20)	AD	DCM	Yes	
	PSEN1 (Presenilin-1,2)	AD	DCM	Yes	Dementia
	BAG3 (BCL2-associated athanogene 3)	AD	DCM	Yes	

^aIndicates that isolated cardiac phenotype can occur in women with the X-linked defects.
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; CDDC, conduction disease with dilated cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HCM+, HCM with preexcitation; HCMc, HCM with conduction disease; LVNC, left ventricular noncompaction; MELAS, (mitochondrial) myopathy, encephalopathy, lactic acidosis, and strokelike episodes syndrome; MERRF, myoclonic epilepsy with ragged red fibers; RCM, restrictive cardiomyopathy.

who carry the same mutation may differ in the severity of cardiomyopathy and associated consequences of rhythm disorders and need for transplantation, indicating the important role of other genetic, epigenetic, and environmental modifiers in disease expression. Sex appears to play a role, as penetrance and clinical severity may be greater in men for most cardiomyopathies. Clinical disease expression is generally more severe in the 3–5% of individuals who harbor two or more mutations linked to cardiomyopathy. However, the clinical course of a patient usually cannot be predicted based on which mutation is present; thus, current therapy is based on the phenotype rather than the genetic defect. Currently, the greatest utility of genetic testing for cardiomyopathy is to inform family evaluations. However, genetic testing occasionally enables the detection of a disease for which specific therapy is indicated, such as the replacements for defective metabolic enzymes in Fabry’s disease and Gaucher disease.

GENES AND PATHWAYS IN CARDIOMYOPATHY

Mutations in sarcomeric genes, encoding the thick and thin myofilament proteins, are the best characterized. While the majority are associated with hypertrophic

cardiomyopathy, an increasing number of sarcomeric mutations have now been implicated in dilated cardiomyopathy, and some in left ventricular noncompaction. Few mutations have been identified in excitation-contraction coupling proteins, perhaps because they are too crucial for survival to allow variation. The most commonly recognized genetic causes of dilated cardiomyopathy are structural mutations of the giant protein titin, encoded TTN, which maintains sarcomere structure and acts as a key signaling molecule.

As cytoskeletal proteins play crucial roles in the structure, connection, and stability of the myocyte, multiple defects in these proteins can lead to cardiomyopathy, usually with a dilated phenotype (Fig. 27-1). For example, desmin forms intermediate filaments that connect the nuclear and plasma membranes, Z-lines, and the intercalated disks between muscle cells. Desmin mutations impair the transmission of force and signaling for both cardiac and skeletal muscle and may cause combined cardiac and skeletal myopathy.

Sarcolemmal membrane protein defects are associated with dilated cardiomyopathy. The best known is dystrophin, encoded by the X chromosome gene DMD, abnormalities of which cause Duchenne’s and Becker’s muscle dystrophy. (Interestingly, abnormal dystrophin can be acquired when the coxsackie virus

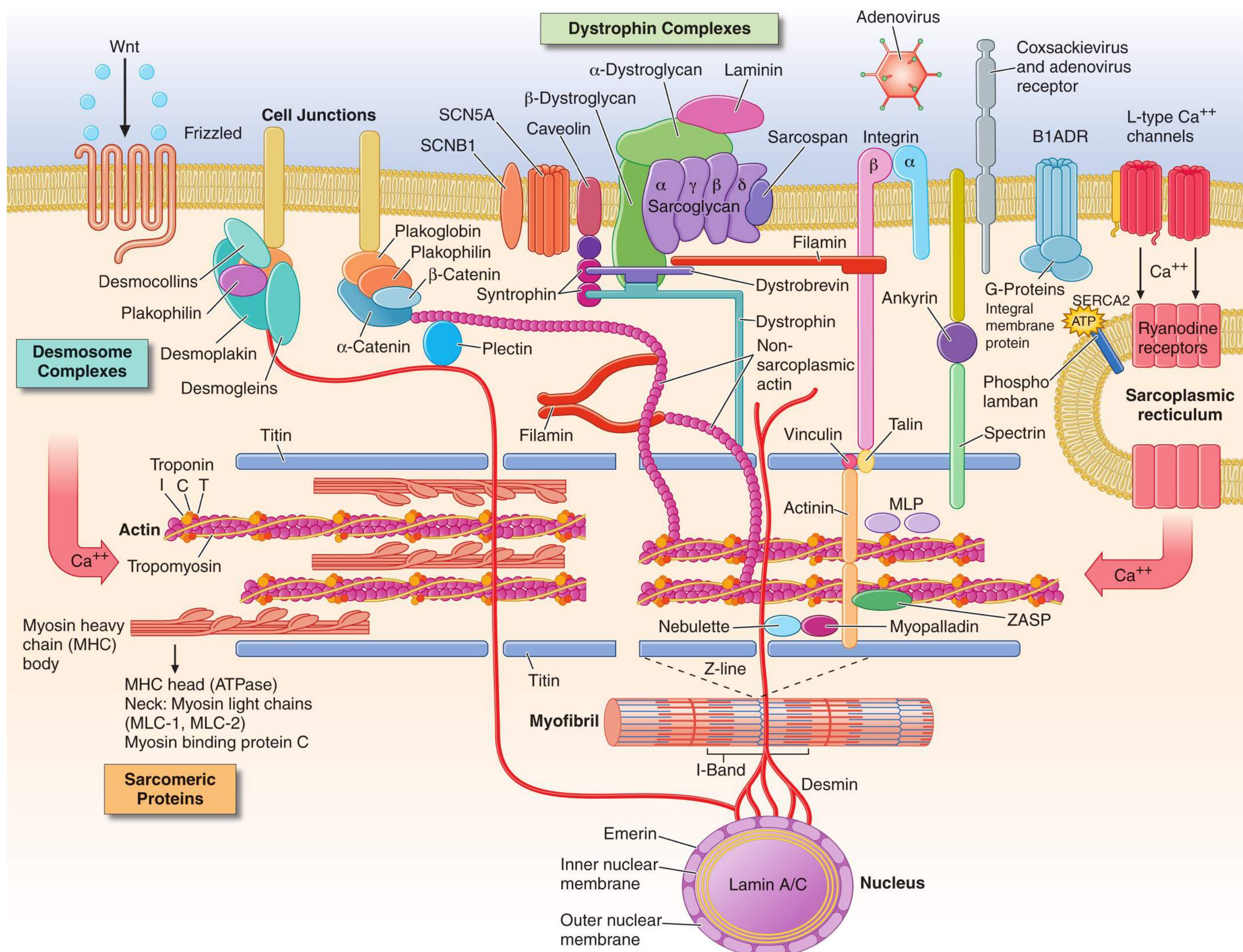


FIGURE 27-1

Drawing of myocyte indicating multiple sites of abnormal gene products associated with cardiomyopathy. Major functional groups include the sarcomeric proteins (actin, myosin, tropomyosin, and the associated regulatory proteins), the dystrophin complex stabilizing and connecting the cell membrane to intracellular

structures, the desmosome complexes associated with cell-cell connections and stability, and multiple cytoskeletal proteins that integrate and stabilize the myocyte. ATP, adenosine triphosphate. (Figure adapted from Jeffrey A. Towbin, MD, University of Cincinnati, with permission.)

cleaves dystrophin during viral myocarditis.) This protein provides a network that supports the sarcolemma and also connects to the sarcomere. The progressive functional defect in both cardiac and skeletal muscle reflects vulnerability to mechanical stress. Dystrophin is associated at the membrane with a complex of other proteins, such as metavinculin, abnormalities of which also cause dilated cardiomyopathy. Defects in the sarcolemmal channel proteins (channelopathies) are generally associated with primary arrhythmias, but mutations in SCN5A, distinct from those that cause the Brugada or long-QT syndromes, have been implicated in dilated cardiomyopathy with conduction disease.

Nuclear membrane protein defects in cardiac and skeletal muscle occur in either autosomal (lamin A/C)

or X-linked (emerin) patterns. These defects are associated with a high prevalence of atrial arrhythmias and conduction system disease, which can occur in some family members without or before detectable cardiomyopathy.

Intercalated disks contribute to intracellular connections, allowing mechanical and electrical coupling between cells and also connections to desmin filaments within the cell. Mutations in proteins of the desmosomal complex compromise attachment of the myocytes, which can become disconnected and die, to be replaced by fat and fibrous tissue. These areas are highly arrhythmogenic and may dilate to form aneurysms. Although more often noted in the right ventricle (arrhythmogenic right ventricular dysplasia), this

condition can affect both ventricles and has also been termed “arrhythmogenic cardiomyopathy.”

Owing to the conservation of signaling pathways in multiple systems, we may expect to discover more extracardiac manifestations of genetic abnormalities initially considered to manifest exclusively in the heart. In contrast, the monogenic disorders of metabolism that affect the heart are already clearly recognized to affect multiple organ systems. Currently, it is most important to diagnose defective enzymes for which specific enzyme replacement therapy can now ameliorate the course of disease, such as with alpha-galactosidase A deficiency (Fabry’s disease). Abnormalities of mitochondrial DNA (maternally transmitted) impair energy production with multiple clinical manifestations, including impaired cognitive function and skeletal myopathy. The phenotypic expression is highly variable depending on the distribution of the maternal mitochondria during embryonic development. Heritable systemic diseases, such as familial amyloidosis and hemochromatosis, can affect the heart without mutation of genes expressed in the heart.

For any patient with suspected or proven genetic disease, family members should be considered and evaluated in a longitudinal fashion. Screening includes an echocardiogram and electrocardiogram (ECG). The indications and implications for confirmatory specific genetic testing vary depending on the specific mutation. The profound questions raised by families about diseases shared and passed down merit serious and sensitive discussion, ideally provided by a trained genetic counselor.

DILATED CARDIOMYOPATHY

An enlarged left ventricle with decreased systolic function as measured by left ventricular ejection fraction characterizes dilated cardiomyopathy (Figs. 27-2, 27-3, and 27-4). Systolic failure is more marked than diastolic dysfunction. Although the syndrome of dilated cardiomyopathy has multiple etiologies (Table 27-4), there appear to be common pathways of secondary response and disease progression. When myocardial injury is acquired, some myocytes may die initially, whereas others survive only to have later programmed cell death (apoptosis), and remaining myocytes hypertrophy in response to increased wall stress. Local and circulating factors stimulate deleterious secondary responses that contribute to progression of disease. Dynamic remodeling of the interstitial scaffolding affects diastolic function and the amount of ventricular dilation. Mitral regurgitation commonly develops as the valvular apparatus is distorted and is usually substantial by the time heart failure is severe. Many cases that present



FIGURE 27-2

Dilated cardiomyopathy. This gross specimen of a heart removed at the time of transplantation shows massive left ventricular dilation and moderate right ventricular dilation. Although the left ventricular wall in particular appears thinned, there is significant hypertrophy of this heart, which weighs more than 800 g (upper limit of normal = 360 g). A defibrillator lead is seen traversing the tricuspid valve into the right ventricular apex. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women’s Hospital, Boston.)

“acutely” have progressed silently through these stages over months to years. Dilation and decreased function of the right ventricle may result from the initial injury and occasionally dominate, but more commonly appear later in relation to mechanical interactions with the failing left ventricle and the elevated afterload presented by secondary pulmonary hypertension.

Regardless of the nature and degree of direct cell injury, the resulting functional impairment often includes some contribution from secondary responses that may be modifiable or reversible. Almost half of all patients with new-onset cardiomyopathy demonstrate substantial spontaneous recovery. Even with long-standing disease, some patients have dramatic improvement to near-normal ejection fractions during pharmacologic therapy, particularly notable with the β -adrenergic antagonists coupled with renin-angiotensin system inhibition. For patients in whom left bundle branch block precedes clinical heart failure by many years, cardiac resynchronization pacing may be particularly likely to improve ejection fraction and decrease ventricular size. Interest in the potential for recovery of cardiomyopathy has been further stimulated by occasional “recovery” of

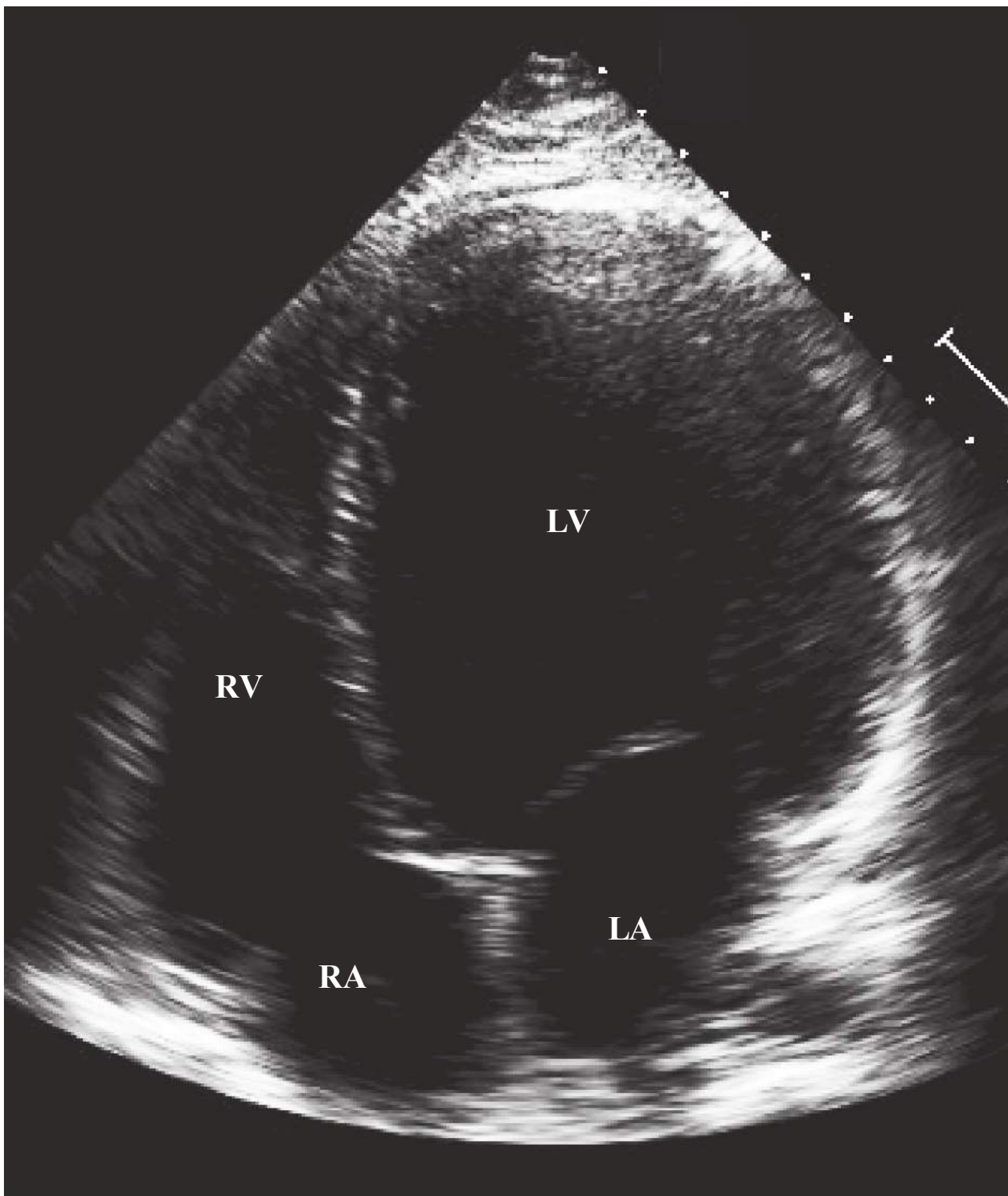


FIGURE 27-3
Dilated cardiomyopathy. This echocardiogram of a young man with dilated cardiomyopathy shows massive global dilation and thinning of the walls of the left ventricle (LV). The left atrium (LA) is also enlarged compared to normal. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. RA, right atrium; RV, right ventricle. (Image courtesy of Justina Wu, MD, Brigham and Women’s Hospital, Boston.)

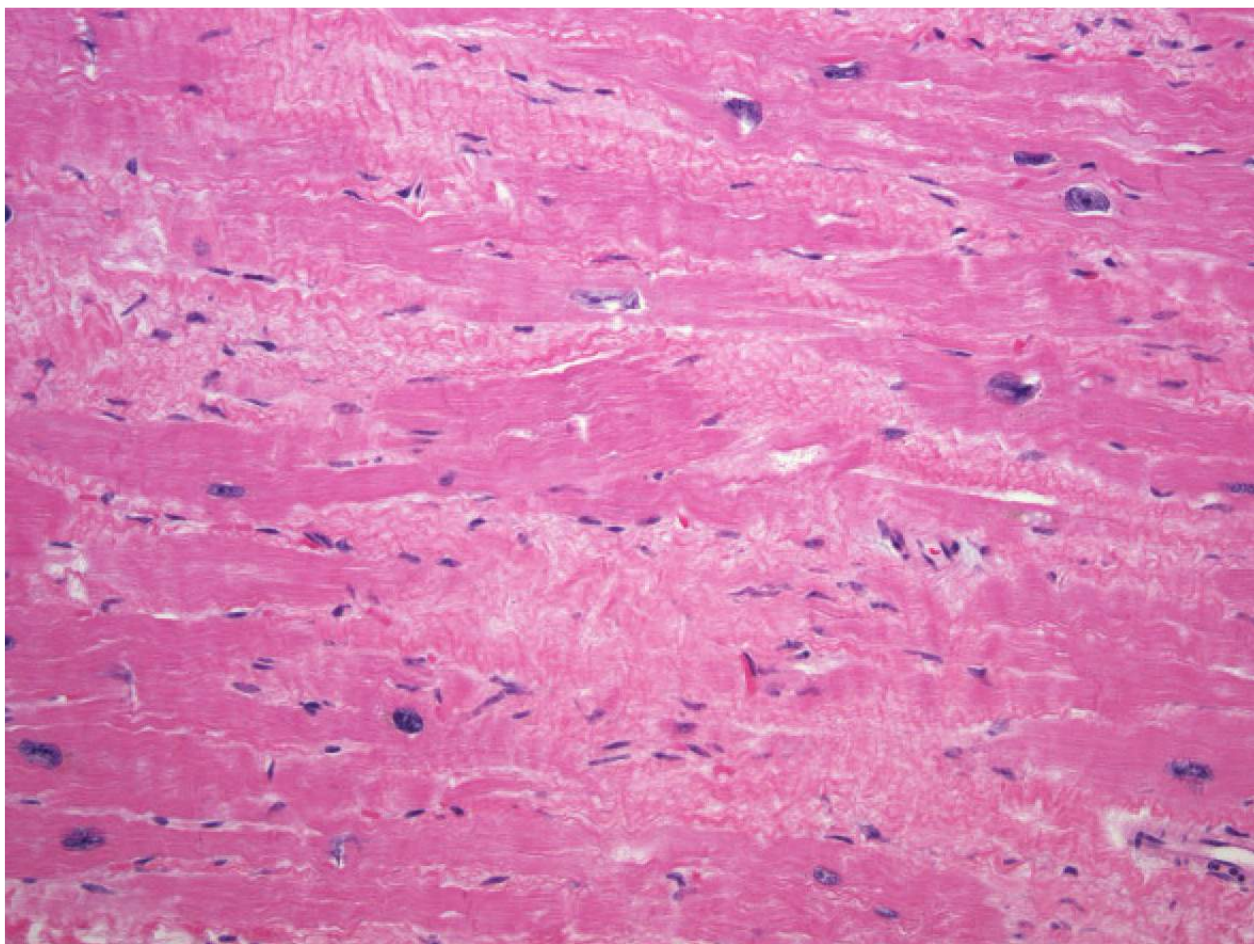


FIGURE 27-4
Dilated cardiomyopathy. Microscopic specimen of a dilated cardiomyopathy showing the nonspecific changes of interstitial fibrosis and myocyte hypertrophy characterized by increased myocyte size and enlarged, irregular nuclei. Hematoxylin and eosin–stained section, 100× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women’s Hospital, Boston.)

TABLE 27-4 MAJOR CAUSES OF DILATED CARDIOMYOPATHY (WITH COMMON EXAMPLES)	
Inflammatory Myocarditis	
Infective	Viral (coxsackie, ^a adenovirus, ^a HIV, hepatitis C) Parasitic (T. cruzi—Chagas’ disease, trypanosomiasis, toxoplasmosis) Bacterial (diphtheria) Spirochetal (Borrelia burgdorferi—Lyme disease) Rickettsial (Q fever) Fungal (with systemic infection)
Noninfective	Granulomatous inflammatory disease Sarcoidosis Giant cell myocarditis Eosinophilic myocarditis Polymyositis, dermatomyositis Collagen vascular disease Peripartum cardiomyopathy Transplant rejection
Toxic	
	Alcohol Catecholamines: amphetamines, cocaine Chemotherapeutic agents (anthracyclines, trastuzumab) Interferon Other therapeutic agents (hydroxychloroquine, chloroquine) Drugs of misuse (emetine, anabolic steroids) Heavy metals: lead, mercury Occupational exposure: hydrocarbons, arsenicals
Metabolic ^a	
	Nutritional deficiencies: thiamine, selenium, carnitine Electrolyte deficiencies: calcium, phosphate, magnesium Endocrinopathy Thyroid disease Pheochromocytoma Diabetes Obesity Hemochromatosis Inherited Metabolic Pathway Defects ^a
Familial ^a (See Table 27-3)	
	Skeletal and cardiac myopathy Dystrophin-related dystrophy (Duchenne’s, Becker’s) Mitochondrial myopathies (e.g., Kearns-Sayre syndrome) Arrhythmogenic ventricular dysplasia Hemochromatosis Associated with other systemic diseases Susceptibility to immune-mediated myocarditis
Overlap with Nondilated Cardiomyopathy	
	“Minimally dilated cardiomyopathy” Hemochromatosis ^a Amyloidosis ^a Hypertrophic cardiomyopathy ^a (“burned-out”) “Idiopathic” ^a

(continued)

TABLE 27-4

MAJOR CAUSES OF DILATED CARDIOMYOPATHY (WITH COMMON EXAMPLES) (CONTINUED)
Miscellaneous (Shared Elements of Above Etiologies)
Arrhythmogenic right ventricular dysplasia (may also affect left ventricle) ^a
Left ventricular noncompaction ^a
Peripartum cardiomyopathy
Tachycardia-related cardiomyopathy
Supraventricular arrhythmias with uncontrolled rate
Very frequent nonsustained ventricular tachycardia or high premature ventricular complex burden
Left bundle branch block (LBBB) has been implicated as a cause of dilated cardiomyopathy appearing late after idiopathic LBBB and responding with near-normal left ventricle size and function after cardiac resynchronization therapy.

^aSome specific cases can be linked now to specific genetic mutation in a familial cardiomyopathy; others with similar phenotypes that appear to be acquired or idiopathic may represent genetic factors not yet identified.

left ventricular function after prolonged mechanical circulatory support. The diagnosis and therapy for dilated cardiomyopathy are generally dictated by the stage of heart failure (**Chap. 19**), with specific aspects discussed for relevant etiologies below.

MYOCARDITIS

Myocarditis (inflammation of the heart) can result from multiple causes but is most commonly attributed to infective agents that can injure the myocardium through direct invasion, production of cardiotoxic substances, or chronic inflammation with or without persistent infection. Myocarditis cannot be assumed from a presentation of decreased systolic function in the setting of an acute infection, as any severe infection causing systemic cytokine release can depress cardiac function transiently. Infectious myocarditis has been reported with almost all types of infective agents but is most commonly associated with viruses and the protozoan *Trypanosoma cruzi*.

INFECTIVE MYOCARDITIS

The pathogenesis of viral myocarditis has been extensively studied in murine models. After viruses gain entry through the respiratory or gastrointestinal tract, they can infect organs possessing specific receptors, such as the coxsackie-adenovirus receptor on the heart. Viral infection and replication can cause myocardial injury and lysis. For example, the enteroviral protease 2A facilitates viral replication and infection through degradation of the myocyte protein dystrophin, which is crucial for myocyte stability. Activation of viral receptor proteins can also activate host tyrosine kinases, which modify the cytoskeleton to facilitate further viral entry.

The first host response to infection is the nonspecific innate immune response, heavily dependent on Toll-like receptors that recognize common antigenic patterns. Cytokine release is rapid, followed by triggered activation and expansion of specific T- and B-cell populations. The initial response appears to be crucial, as early immunosuppression in animal models can increase viral replication and worsen cardiac injury. However, successful recovery from viral infection depends not only on the efficacy of the immune response to limit viral infection, but also on timely downregulation to prevent overreaction and autoimmune injury to the host.

The secondary acquired immune response is more specifically addressed against the viral proteins and can include both T-cell infiltration and antibodies to viral proteins. If unchecked, the acquired immune response can perpetuate secondary cardiac damage. Ongoing cytokine release activates matrix metalloproteinases that can disrupt the collagen and elastin scaffolding of the heart, potentiating ventricular dilation. Stimulation of profibrotic factors leads to pathologic interstitial fibrosis. Some of the antibodies triggered through co-stimulation or molecular mimicry also recognize targets within the host myocyte, such as the β -adrenergic receptor, troponin, and Na^+/K^+ ATPase, but it remains unclear whether these antibodies contribute actively to cardiac dysfunction in humans or merely serve as markers of cardiac injury.

It is not known how long the viruses persist in the human heart, whether late persistence of the viral genome continues to be deleterious, or how often a dormant virus can again become pathogenic. Genomes of common viruses have frequently been detected in patients with clinical diagnoses of myocarditis or dilated cardiomyopathy, but there is little information on how often these are present in patients without cardiac disease (see below). Further information is needed to understand the relative timing and contribution of infection, immune responses, and secondary adaptations in the progression of heart failure after viral myocarditis (**Fig 27-5**).

Clinical presentation of viral myocarditis

Acute viral myocarditis often presents with symptoms and signs of heart failure. Some patients present with chest pain suggestive of pericarditis or acute myocardial infarction. Occasionally, the presentation is dominated by atrial or ventricular tachyarrhythmias, or by pulmonary or systemic emboli from intracardiac thrombi. Electrocardiographic or echocardiographic abnormalities may also be detected incidentally during evaluation for other diagnoses. The typical patient with presumed viral myocarditis is a young to middle-aged adult who develops progressive dyspnea and weakness within a few days to weeks after a viral syndrome that was accompanied by fever and myalgias.

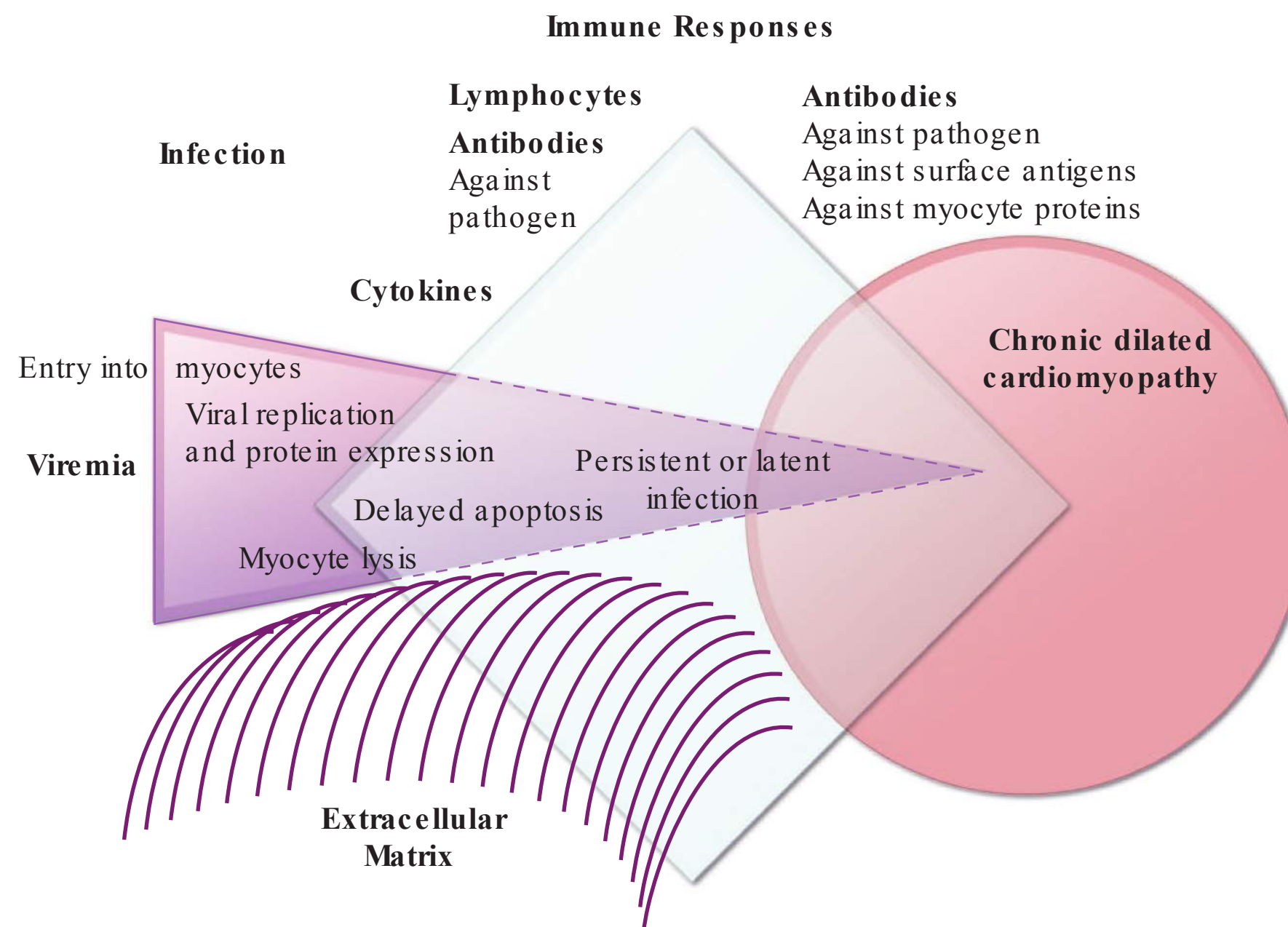


FIGURE 27-5

Schematic diagram demonstrating the possible progression from infection through direct, secondary, and autoimmune responses to dilated cardiomyopathy. Most of the supporting evidence for this sequence is derived from animal models. It is

not known to what degree persistent infection and/or ongoing immune responses contribute to ongoing myocardial injury in the chronic phase.

A small number of patients present with fulminant myocarditis, with rapid progression from a severe febrile respiratory syndrome to cardiogenic shock that may involve multiple organ systems, leading to renal failure, hepatic failure, and coagulopathy. These patients are typically young adults who have recently been dismissed from urgent care settings with antibiotics for bronchitis or oseltamivir for viral syndromes, only to return within a few days in rapidly progressive cardiogenic shock. Prompt triage is vital to provide aggressive support with high-dose intravenous catecholamine therapy and sometimes with temporary mechanical circulatory support. Recognition of patients with this fulminant presentation is potentially life-saving as more than half can survive, with marked improvement demonstrable within the first few weeks. The ejection fraction function of these patients often recovers to near-normal, although residual diastolic dysfunction may limit vigorous exercise for some survivors.

Chronic viral myocarditis is often invoked, but rarely proven, as a diagnosis when no other cause of dilated cardiomyopathy can be identified. However, some cases of otherwise unexplained cardiomyopathy will later be recognized to have a genetic basis, or ultimately found to have resulted from excess alcohol consumption or illicit drugs. There are likely many other causes that cannot yet be identified. The prevalence of previous or persistent viral infection as the cause for chronic dilated cardiomyopathy remains highly controversial.

Laboratory evaluation for myocarditis

The initial evaluation for suspected myocarditis includes an ECG, an echocardiogram, and serum levels of troponin and creatine phosphokinase fractions. Magnetic resonance imaging is increasingly used for the diagnosis of myocarditis, which is supported by evidence of increased tissue edema and gadolinium enhancement (**Fig. 27-6**), particularly in the mid-wall (as distinct from usual coronary artery territories).

Endomyocardial biopsy is not often indicated for the initial evaluation of suspected viral myocarditis unless ventricular tachyarrhythmias suggest possible etiologies of sarcoidosis or giant cell myocarditis. The indications and benefit of endomyocardial biopsy for evaluation of myocarditis or new-onset cardiomyopathy remain controversial.

The Dallas Criteria for myocarditis on endomyocardial biopsy include lymphocytic infiltrate with evidence of myocyte necrosis (**Fig. 27-7**) and are negative in 80–90% of patients with clinical myocarditis. Negative Dallas Criteria can reflect sampling error or early resolution of lymphocytic infiltrates, but also the insensitivity of the test when inflammation results from cytokines and antibody-mediated injury. Routine histologic examination of endomyocardial biopsy rarely reveals a specific infective etiology, such as toxoplasmosis or Cytomegalovirus. Immunohistochemistry of myocardial biopsy samples is commonly used to identify active lymphocyte subtypes and may also detect upregulation

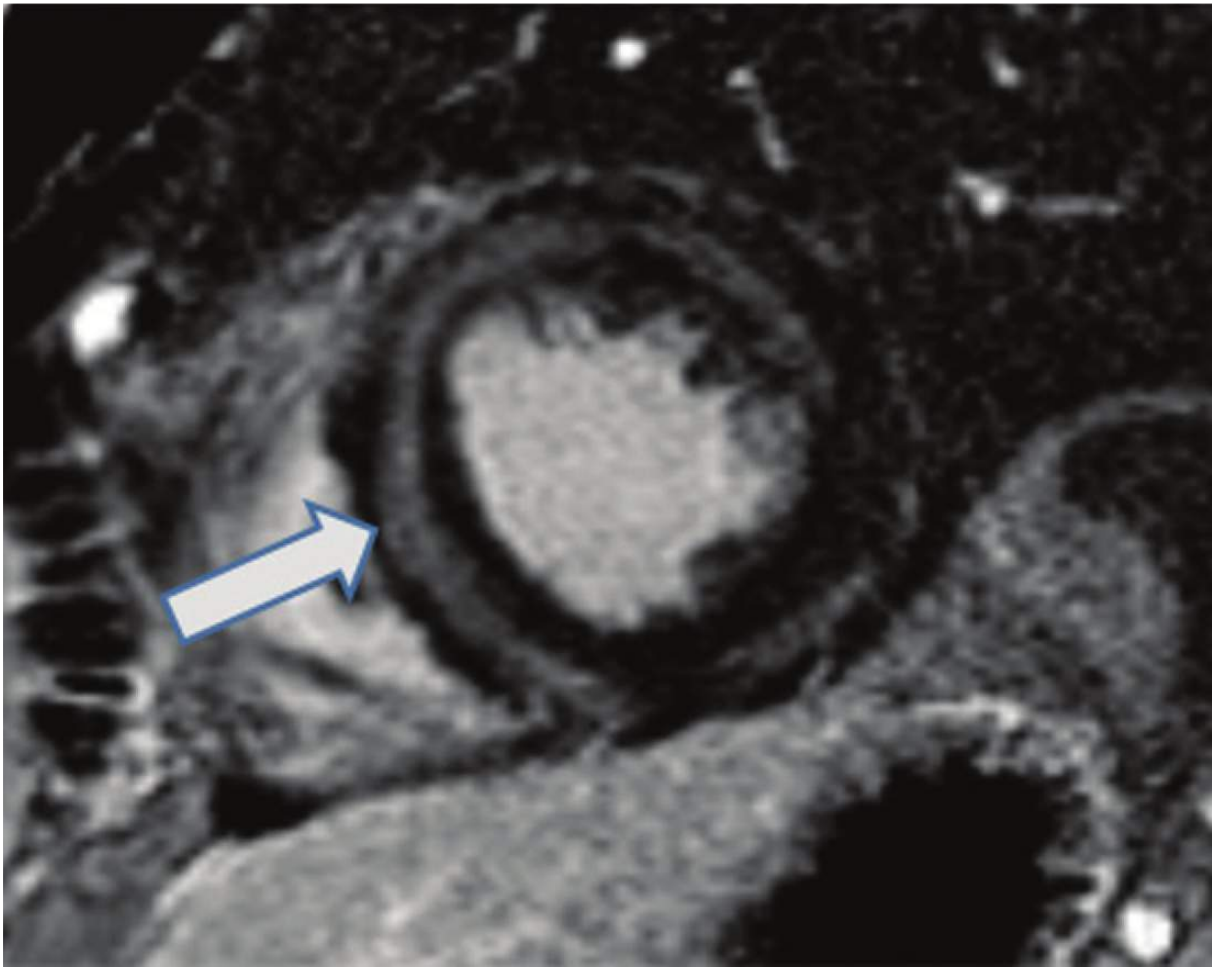


FIGURE 27-6

Magnetic resonance image of myocarditis showing the typical mid-wall location (arrow) for late gadolinium enhancement from cardiac inflammation and scarring. (Image courtesy of Ron Blankstein, MD, and Marcelo Di Carli, MD, Division of Nuclear Medicine, Brigham and Women's Hospital, Boston.)

of HLA antigens and the presence of complement components attributed to inflammation, but the specificity and significance of these findings are uncertain.

An increase in circulating viral titers between acute and convalescent blood samples supports a diagnosis of acute viral myocarditis with potential spontaneous improvement. There is no established role for measuring circulating anti-heart antibodies, which may be the

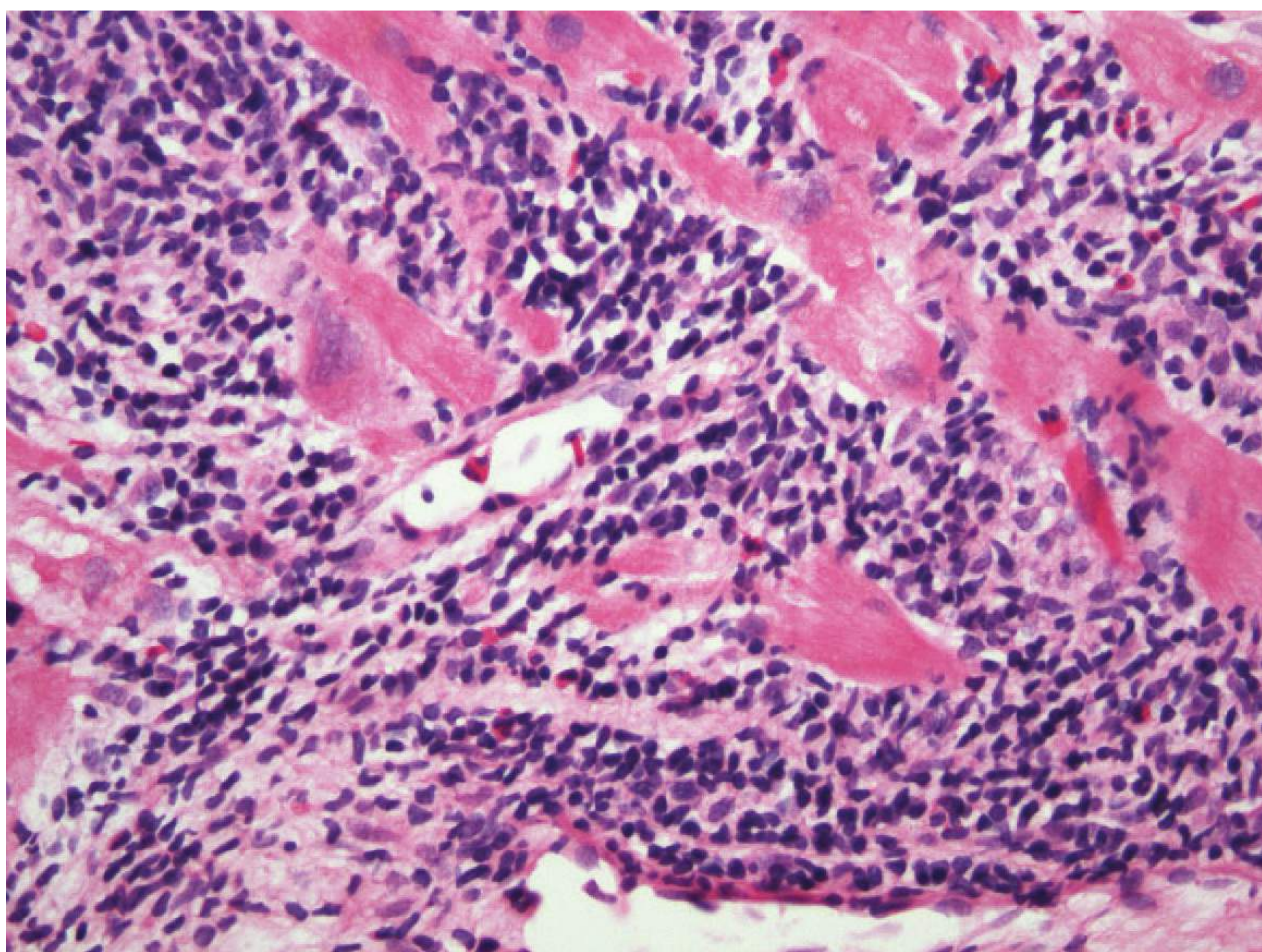


FIGURE 27-7

Acute myocarditis. Microscopic image of an endomyocardial biopsy showing massive infiltration with mononuclear cells and occasional eosinophils associated with clear myocyte damage. The myocyte nuclei are enlarged and reactive. Such extensive involvement of the myocardium would lead to extensive replacement fibrosis even if the inflammatory response could be suppressed. Hematoxylin and eosin–stained section, 200× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

result, rather than a cause, of myocardial injury and have been found also in patients with coronary artery disease and genetic cardiomyopathy.

Patients with recent or ongoing viral syndromes can be classified into three levels of diagnosis:

1. Possible subclinical acute myocarditis is diagnosed when a patient has a typical viral syndrome but no cardiac symptoms, with one or more of the following:
 - Elevated biomarkers of cardiac injury (troponin or CK-MB)
 - ECG findings suggestive of acute injury
 - Reduced left ventricular ejection fraction or regional wall motion
 - Abnormality on cardiac imaging, usually echocardiography
2. Probable acute myocarditis is diagnosed when the above criteria are met and accompanied also by cardiac symptoms, such as shortness of breath or chest pain, which can result from pericarditis or myocarditis. When clinical findings of pericarditis (pleuritic chest pain, ECG abnormalities, pericardial rub or effusion) are accompanied by elevated troponin or CK-MB or abnormal cardiac wall motion, the terms perimyocarditis or myopericarditis are sometimes used.
3. Definite myocarditis is diagnosed when there is histologic or immunohistologic evidence of inflammation on endomyocardial biopsy (see below) and does not require any other laboratory or clinical criteria.

SPECIFIC VIRUSES IMPLICATED IN MYOCARDITIS

In humans, viruses are often suspected but rarely proven to be the direct cause of clinical myocarditis. First implicated was the picornavirus family of RNA viruses, principally the enteroviruses, coxsackie virus, echovirus, and poliovirus. Influenza, another RNA virus, is implicated with varying frequency every winter and spring as epitopes change. Of the DNA viruses, adenovirus, vaccinia (smallpox vaccine), and the herpesviruses (varicella zoster, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 [HHV6]) are well-recognized to cause myocarditis but also occur commonly in the healthy population. Polymerase chain reaction (PCR) detects viral genomes in the majority of patients with dilated cardiomyopathy, but also in normal “control” hearts. Most often detected are parvovirus B19 and HHV6, which may affect the cardiovascular system, in part, through infection of vascular endothelial cells. However, their contribution to chronic cardiomyopathy is uncertain, as serologic evidence of exposure is present in many children and most adults.

Human immunodeficiency virus (HIV) was associated with an incidence of dilated cardiomyopathy of 1–2%; however, with the advent of highly active antiretroviral

therapy (HAART), HIV has been associated with a significantly lower incidence of cardiac disease. Cardiomyopathy in HIV may result from cardiac involvement with other associated viruses, such as cytomegalovirus and hepatitis C, as well as by HIV directly. Antiviral drugs to treat chronic HIV can cause cardiomyopathy, both directly and through drug hypersensitivity. The clinical picture may be complicated by pericardial effusions and pulmonary hypertension. There is a high frequency of lymphocytic myocarditis found at autopsy, and viral particles have been demonstrated in the myocardium in some cases, consistent with direct causation.

Hepatitis C has been repeatedly implicated in cardiomyopathy, particularly in Germany and Asia. Cardiac dysfunction may improve after interferon therapy. As this cytokine itself often depresses cardiac function transiently, careful coordination of administration and ongoing clinical evaluation are critical. Involvement of the heart with hepatitis B is uncommon, but can be seen when associated with systemic vasculitis (polyarteritis nodosa).

Additional viruses implicated specifically in myocarditis include mumps, respiratory syncytial virus, the arboviruses (dengue fever and yellow fever), and arenaviruses (Lassa fever). However, for any serious infection, the systemic inflammatory response can cause nonspecific depression of cardiac function, which is generally reversible if the patient survives.

THERAPY

There is currently no specific therapy recommended during any stage of viral myocarditis. During acute infection, therapy with anti-inflammatory or immunosuppressive medications is avoided, as their use has been shown to increase viral replication and myocardial injury in animal models. Therapy with specific antiviral agents (such as oseltamivir) has not been studied in relation to cardiac involvement. There is ongoing investigation into the impact of antiviral therapy to treat chronic viral persistence identified from endomyocardial biopsy. Large trials of immunosuppressive therapy for Dallas Criteria-positive myocarditis have been negative. There are some initial encouraging results and ongoing investigations with immunosuppressive therapy for immune-mediated myocarditis defined by immunohistologic criteria on biopsy or circulating anti-heart antibodies in the absence of myocardial viral genomes. However, neither antiviral nor anti-inflammatory therapies are currently recommended. Until we have a better understanding of the different phases of viral myocarditis and its sequelae and the effects of timed or targeted therapies, treatment will continue to be directed to the clinical cardiovascular stage of the disease, for dilated cardiomyopathy in general.

Parasitic myocarditis

Chagas' disease is the third most common parasitic infection in the world and the most common infective cause of cardiomyopathy. The protozoan *T. cruzi* is transmitted by the bite of the reduviid bug, endemic in the rural areas of South and Central America. Transmission can also occur through blood transfusion, organ donation, from mother to fetus, and occasionally orally. While programs to eradicate the insect vector have decreased the prevalence from about 16 million to less than 10 million in South America, cases are increasingly recognized in Western developed countries. Approximately 100,000 affected individuals are currently living in the United States, most of whom contracted the disease in endemic areas.

Multiple pathogenic mechanisms are implicated. The parasite itself can cause myocyte lysis and primary neuronal damage, and specific immune responses may recognize the parasites or related antigens and lead to chronic immune activation in the absence of detectable parasites. Molecular techniques have revealed persistent parasite DNA fragments in infected individuals. Further evidence for persistent infection is the eruption of parasitic skin lesions during immunosuppression after cardiac transplantation. As with viral myocarditis, the relative roles of persistent infection and of secondary autoimmune injury have not been resolved (Fig. 27-5). An additional factor in the progression of Chagas' disease is the autonomic dysfunction and microvascular damage that may contribute to cardiac and gastrointestinal disease.

The acute phase of Chagas' disease with parasitemia is usually unrecognized, but in fewer than 5% of cases, it presents clinically within a few weeks of infection, with nonspecific symptoms or occasionally with acute myocarditis and meningoencephalitis. In the absence of antiparasitic therapy, the silent stage progresses slowly over 10–30 years in almost half of patients to manifest in the cardiac and gastrointestinal systems in the chronic stages. Features typical of Chagas' disease are conduction system abnormalities, particularly sinus node and atrioventricular (AV) node dysfunction and right bundle branch block. Atrial fibrillation and ventricular tachyarrhythmias also occur. Small ventricular aneurysms are common, particularly at the ventricular apex. These dilated ventricles are particularly thrombogenic, giving rise to pulmonary and systemic emboli. Xenodiagnosis, detection of the parasite itself, is rarely performed. The serologic tests for specific IgG antibodies against the trypanosome lack sufficient specificity and sensitivity, thereby requiring two separate positive tests required to make a diagnosis.

Treatment of the advanced stages focuses on clinical manifestations of the disease and includes heart failure medications, pacemaker-defibrillators, and

anticoagulation. Increasing attention is directed to antiparasitic therapy even in chronic disease without obvious active infection. The most common effective antiparasitic therapies are benznidazole and nifurtimox, both associated with multiple severe reactions, including dermatitis, gastrointestinal distress, and neuropathy. Survival is less than 30% at 5 years after the onset of overt clinical heart failure. Patients without major extracardiac disease have occasionally undergone transplantation, after which they may require lifelong therapy to suppress reactivation of infection.

African trypanosomiasis infection results from the tsetse fly bite and can occur in travelers exposed during trips to Africa. The West African form is caused by *Trypanosoma brucei gambiense* and progresses silently over years. The East African form caused by *T. brucei rhodesiense* can progress rapidly through perivascular infiltration to myocarditis and heart failure, with frequent arrhythmias. The diagnosis is made by identification of trypanosomes in blood, lymph nodes, or other affected sites. Antiparasitic therapy has limited efficacy and is determined by the specific type and the stage of infection (hemolymphatic or neurologic).

Toxoplasmosis is contracted through undercooked infected beef or pork, transmission from feline feces, organ transplantation, transfusion, or maternal-fetal transmission. Immunocompromised hosts are most likely to experience reactivation of latent infection from cysts. The cysts have been found in up to 40% of autopsies of patients dying from HIV infection. Toxoplasmosis may present with encephalitis or chorioretinitis and, in the heart, can cause myocarditis, pericardial effusion, constrictive pericarditis, and heart failure. The diagnosis in an immunocompetent patient is made when the IgM is positive and the IgG becomes positive later. Active toxoplasmosis may be suspected in an immunocompromised patient with myocarditis and a positive IgG titer for toxoplasmosis, particularly when avidity testing identifies high specificity of the antibody. Fortuitous sampling occasionally reveals the cysts in the myocardium. Combination therapy can include pyrimethamine and sulfadiazine or clindamycin.

Trichinellosis is caused by *Trichinella spiralis* larva ingested with undercooked meat. Larvae migrating into skeletal muscles cause myalgias, weakness, and fever. Periorbital and facial edema and conjunctival and retinal hemorrhage may also be seen. Although the larva may occasionally invade the myocardium, clinical heart failure is rare and, when observed, attributed to the eosinophilic inflammatory response. The diagnosis is made from the specific serum antibody and is further supported by the presence of eosinophilia. Treatment includes antihelminthic drugs (albendazole, mebendazole) and glucocorticoids if inflammation is severe.

Cardiac involvement with *Echinococcus* is rare, but cysts can form and rupture in the myocardium and pericardium.

Bacterial infections

Most bacterial infections can involve the heart occasionally through direct invasion and abscess formation, but do so rarely. More commonly, systemic inflammatory responses depress contractility in severe infection and sepsis. Diphtheria specifically affects the heart in almost one-half of cases, and cardiac involvement is the most common cause of death in patients with this infection. The prevalence of vaccines has shifted the incidence of diphtheria from children worldwide to countries without routine immunization and to older populations who have lost their immunity. The bacillus releases a toxin that impairs protein synthesis and may particularly affect the conduction system. The specific antitoxin should be administered as soon as possible, with higher priority than antibiotic therapy. Other systemic bacterial infections that can involve the heart include brucellosis, chlamydophila, legionella, meningococcus, mycoplasma, psittacosis, and salmonellosis, for which specific treatment is directed at the systemic infection.

Clostridial infections cause myocardial damage from the released toxin. Gas bubbles can be detected in the myocardium, and occasionally abscesses can form in the myocardium and pericardium. Streptococcal infection with β -hemolytic streptococci is most commonly associated with acute rheumatic fever and is characterized by inflammation and fibrosis of cardiac valves and systemic connective tissue, but it can also lead to a myocarditis with focal or diffuse infiltrates of mononuclear cells.

Tuberculosis can involve the myocardium directly as well as through tuberculous pericarditis, but rarely does so when the disease is treated with antibiotics. Whipple's disease is caused by *Tropheryma whipplei*. The usual manifestations are in the gastrointestinal tract, but pericarditis, coronary arteritis, valvular lesions, and occasionally clinical heart failure may also occur. Multidrug antituberculous regimens are effective, but the disease tends to relapse even with appropriate treatment.

Other infections

Spirochetal myocarditis has been diagnosed from myocardial biopsies containing *Borrelia burgdorferi* that causes Lyme disease. Lyme carditis most often presents with arthritis and conduction system disease that resolves within 1–2 weeks of antibiotic treatment, only rarely implicated in chronic heart failure.

Fungal myocarditis can occur due to hematogenous or direct spread of infection from other sites, as has been described for aspergillosis, actinomycosis,

blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, and mucormycosis. However, cardiac involvement is rarely the dominant clinical feature of these infections.

The **rickettsial infections**, Q fever, Rocky Mountain spotted fever, and scrub typhus are frequently accompanied by ECG changes, but most clinical manifestations relate to systemic vascular involvement.

NONINFECTIVE MYOCARDITIS

Myocardial inflammation can occur without apparent preceding infection. The paradigm of noninfective inflammatory myocarditis is cardiac transplant rejection, from which we have learned that myocardial depression can develop and reverse quickly, that non-cellular mediators such as antibodies and cytokines play a major role in addition to lymphocytes, and that myocardial antigens are exposed by prior physical injury and viral infection.

The most commonly diagnosed noninfective inflammation is granulomatous myocarditis, including both sarcoidosis and giant cell myocarditis. Sarcoidosis is a multisystem disease most commonly affecting the lungs. Although classically presenting with higher prevalence in young African-American men, the epidemiology appears to be changing, with increasing recognition of sarcoidosis in Caucasian patients in nonurban areas. Patients with pulmonary sarcoid are at high risk for cardiac involvement, but cardiac sarcoidosis also occurs without clinical lung disease. Regional clustering of the disease supports the suspicion that the granulomatous reaction is triggered by an infectious or environmental allergen not yet identified.

The sites and density of cardiac granulomata, the time course, and the degree of extracardiac involvement are remarkably variable. Patients may present with rapid-onset heart failure and ventricular tachyarrhythmias, conduction block, chest pain syndromes, or minor cardiac findings in the setting of ocular involvement, an infiltrative skin rash, or a nonspecific febrile illness. They may also present less acutely after months to years of fluctuating cardiac symptoms. When ventricular tachycardia or conduction block dominates the initial presentation of heart failure without coronary artery disease, suspicion should be high for these granulomatous myocarditides.

Depending on the time course, the ventricles may appear restrictive or dilated. There is often right ventricular predominance of both dilation and ventricular arrhythmias, sometimes initially attributed to arrhythmogenic right ventricular dysplasia. Small ventricular aneurysms are common. Computed tomography of the chest often reveals pulmonary lymphadenopathy even in the absence of clinical lung disease. Metabolic imaging (positron emission tomography (PET)) of the whole

chest can highlight active sarcoid lesions that are avid for glucose. Magnetic resonance imaging (MRI) of the heart can identify areas likely to be inflammatory. To rule out chronic infections, such as tuberculosis or histoplasmosis as the cause of adenopathy, the diagnosis usually requires pathologic confirmation. Biopsy of enlarged mediastinal nodes may provide the highest yield. The scattered granulomata of sarcoidosis can easily be missed on cardiac biopsy (**Fig. 27-8**).

Immunosuppressive treatment for sarcoidosis is initiated with high-dose glucocorticoids, which are often more effective for arrhythmias than for the heart failure. Patients with sarcoid lesions that persist or recur during tapering of corticosteroids are considered candidates for other immunosuppressive therapies, frequently with agents also used for cardiac transplantation. Pacemakers and implantable defibrillators are generally indicated to prevent life-threatening heart block or ventricular tachycardia, respectively. Because the inflammation often resolves into extensive fibrosis that impairs cardiac function and provides pathways for reentrant arrhythmias, the prognosis for improvement is best when the granulomata are not extensive and the ejection fraction is not severely reduced.

Giant cell myocarditis is less common than sarcoidosis, but accounts for 10–20% of biopsy-positive cases of myocarditis. Giant cell myocarditis typically presents with rapidly progressive heart failure and tachyarrhythmias. Diffuse granulomatous lesions are surrounded by extensive inflammatory infiltrate unlikely to be missed on endomyocardial biopsy, often with extensive eosinophilic infiltration. Associated conditions are thymomas,

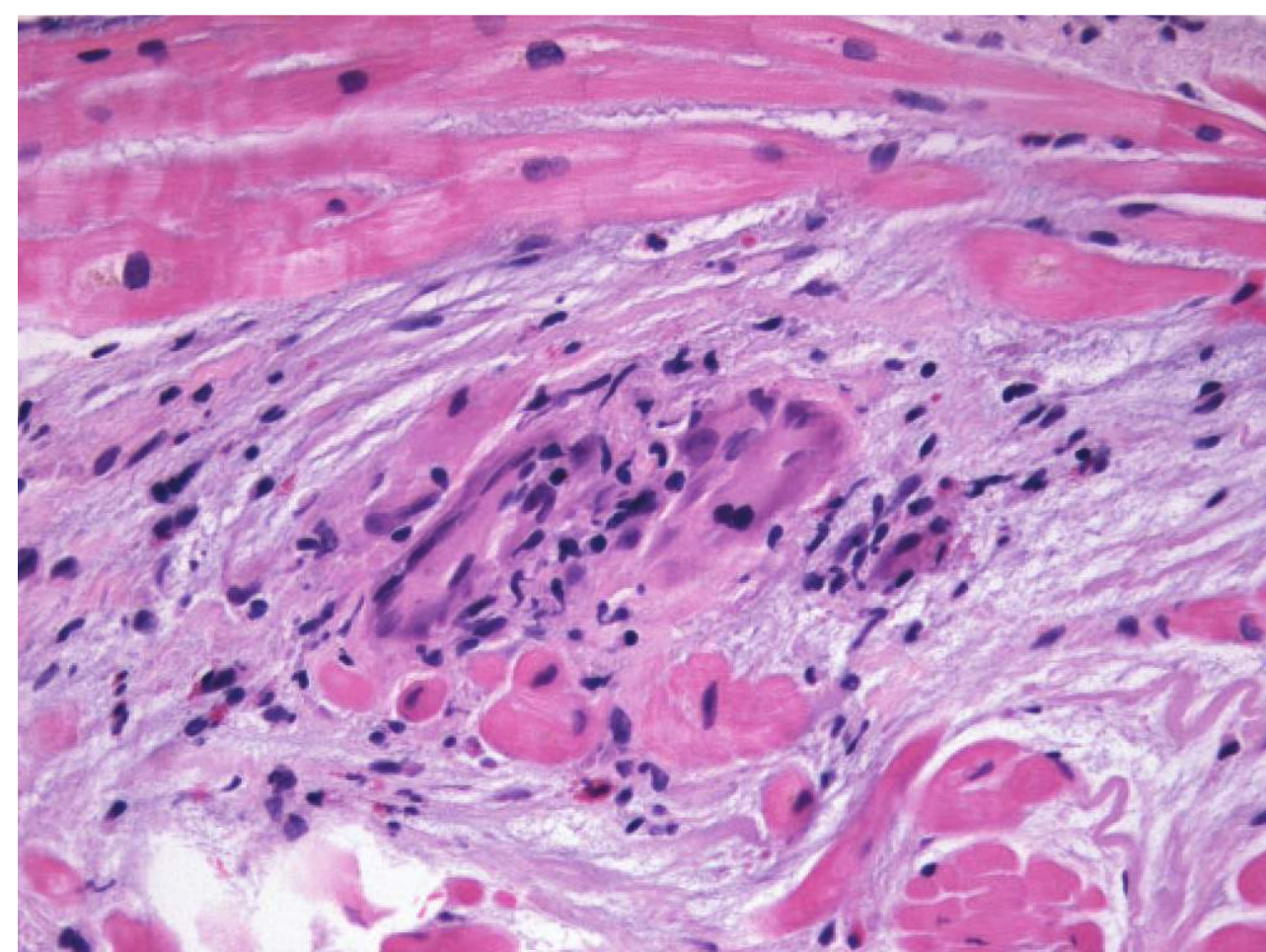


FIGURE 27-8

Sarcoidosis. Microscopic image of an endomyocardial biopsy showing a noncaseating granuloma and associated interstitial fibrosis typical of sarcoidosis. No microorganisms were present on special stains, and no foreign material was identified. Hematoxylin and eosin–stained section, 200× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

thyroiditis, pernicious anemia, other autoimmune diseases, and occasionally recent infections. Glucocorticoid therapy is less effective than for sarcoidosis and is sometimes combined with other immunosuppressive agents. The course is generally of rapid deterioration requiring urgent transplantation. Although the severity of presentation and myocardial histology are more fulminant than with sarcoidosis, the occasional finding of giant cell myocarditis after sarcoidosis suggests that they may in some cases represent different stages of the same disease spectrum.

Eosinophilic myocarditis can be an important manifestation of the hypereosinophilic syndrome, which in Western countries is often idiopathic, although in Mediterranean and African countries, it is likely a consequence of antecedent infection. It may also be seen with systemic eosinophilic syndromes such as Churg-Strauss syndrome or malignancies. Hypersensitivity myocarditis is often an unexpected diagnosis, made when the biopsy reveals infiltration with lymphocytes and mononuclear cells with a high proportion of eosinophils. Most commonly, the reaction is attributed to antibiotics, particularly those taken chronically, but thiazides, anticonvulsants, indomethacin, and methyldopa have also been implicated. Occasional associations with the smallpox vaccine have been reported. Although the circulating eosinophil count may be slightly elevated in hypersensitivity myocarditis, it does not reach the high levels of the hypereosinophilic syndrome. High-dose glucocorticoids and discontinuation of the trigger agent can be curative for hypersensitivity myocarditis.

Myocarditis is often associated with systemic inflammatory diseases, such as polymyositis and dermatomyositis, which affect skeletal and cardiac muscle. Although noninfective inflammatory myocarditis is sometimes included in the differential diagnosis of cardiac findings in patients with connective tissue disease such as systemic lupus erythematosus, pericarditis, vasculitis, pulmonary hypertension, and accelerated coronary artery disease are more common cardiac manifestations of connective tissue disease.

Peripartum cardiomyopathy (PPCM) develops during the last trimester or within the first 6 months after pregnancy, with a frequency between 1:2000 and 1:15,000 deliveries. Risk factors are increased maternal age, increased parity, twin pregnancy, malnutrition, use of tocolytic therapy for premature labor, and preeclampsia or toxemia of pregnancy. Heart failure early after delivery was previously common in Nigeria, when the custom for new mothers included salt ingestion while reclining on a warm bed, which likely impaired mobilization of the excess circulating volume after delivery. In the Western world, lymphocytic myocarditis has sometimes been found on myocardial biopsy. This inflammation has been hypothesized to reflect increased susceptibility to viral myocarditis or

an autoimmune myocarditis due to cross-reactivity of anti-uterine antibodies against cardiac muscle. Another proposed mechanism invokes an abnormal prolactin cleavage fragment, which is induced by oxidative stress and may trigger myocardial apoptosis; this observation has led to preliminary investigation of bromocriptine as possible therapy.

Very recently, PPCM has been found to be associated with increased antiangiogenic signaling, a process that is exacerbated by preeclampsia. In animal models of this disease, proangiogenic therapies have proven curative.

As the increased circulatory demand of pregnancy can aggravate other cardiac disease that was clinically unrecognized, it is crucial to the diagnosis of PPCM that there be no evidence for a preexisting cardiac disorder. By contrast, heart failure presenting earlier in pregnancy has been termed pregnancy-associated cardiomyopathy (PACM). Both PPCM and PACM have been found in some families with other presentations of dilated cardiomyopathy, in some cases with known sarcomeric protein mutations. Pregnancy may, thus, represent an environmental trigger for accelerated phenotypic expression of genetic cardiomyopathy.

TOXIC CARDIOMYOPATHY

Cardiotoxicity has been reported with multiple environmental and pharmacologic agents. Often these associations are seen only with very high levels of exposure or acute overdoses, in which acute electrocardiographic and hemodynamic abnormalities may reflect both direct drug effect and systemic toxicity.

Alcohol is the most common toxin implicated in chronic dilated cardiomyopathy. Excess consumption may contribute to more than 10% of cases of heart failure, including exacerbation of cases with other primary etiologies such as valvular disease or previous infarction. Toxicity is attributed both to alcohol and to its primary metabolite, acetaldehyde. Polymorphisms of the genes encoding alcohol dehydrogenase and the angiotensin-converting enzyme increase the likelihood of alcoholic cardiomyopathy in an individual with excess consumption. Superimposed vitamin deficiencies and toxic alcohol additives are rarely implicated. The alcohol consumption necessary to produce cardiomyopathy in an otherwise normal heart has been estimated to be five to six drinks (about 4 ounces of pure ethanol) daily for 5–10 years, but frequent binge drinking may also be sufficient. Many patients with alcoholic cardiomyopathy are fully functional in their daily lives without apparent stigmata of alcoholism. The cardiac impairment in severe alcoholic cardiomyopathy is the sum of both permanent damage and a substantial component that is reversible after cessation of alcohol consumption. Atrial fibrillation occurs commonly both early in the disease (“holiday heart”) and in advanced stages. Medical

therapy includes neurohormonal antagonists and diuretics as needed for fluid management. Withdrawal should be supervised to avoid exacerbations of heart failure or arrhythmias, and ongoing support arranged. Even with severe disease, marked improvement can occur within 3–6 months of abstinence. Implantable defibrillators are generally deferred until an adequate period of abstinence, after which they may not be necessary if the ejection fraction has improved. With continued consumption, the prognosis is grim.

Cocaine, amphetamines, and related catecholaminergic stimulants can produce chronic cardiomyopathy as well as acute ischemia and tachyarrhythmias. Pathology reveals microinfarcts consistent with small vessel ischemia, similar to those seen with pheochromocytoma.

Chemotherapy agents are the most common drugs implicated in toxic cardiomyopathy. Judicious use of these drugs requires balancing the risks of the malignancy and the risks of cardiotoxicity, as many cancers have a chronic course with better prognosis than heart failure.

Anthracyclines cause characteristic histologic changes of vacuolar degeneration and myofibrillar loss. Generation of reactive oxygen species involving heme compounds is currently the favored explanation for myocyte injury and fibrosis. Disruption of the large titin protein may contribute to loss of sarcomere organization. Risk for cardiotoxicity increases with higher doses, preexisting cardiac disease, and concomitant chest irradiation. There are three different presentations of anthracycline-induced cardiomyopathy. (1) Heart failure can develop acutely during administration of a single dose, but may clinically resolve in a few weeks. (2) Early-onset doxorubicin cardiotoxicity develops in about 3% of patients during or shortly after a chronic course, relating closely to total dose. It may be rapidly progressive, but may also resolve to good, but not normal, ventricular function. (3) The chronic presentation differs according to whether therapy was given before or after puberty. Patients who received doxorubicin while still growing may have impaired development of the heart, which leads to clinical heart failure by the time the patient reaches the early twenties. Late after adult exposure, patients may develop the gradual onset of symptoms or an acute onset precipitated by a reversible second insult, such as influenza or atrial fibrillation. Doxorubicin cardiotoxicity leads to a relatively nondilated ventricle, perhaps due to the accompanying fibrosis. Thus, the stroke volume may be severely reduced with an ejection fraction of 30–40%, which would be well tolerated in a patient with a larger ventricle typical of other cardiomyopathies with systolic dysfunction. Therapy includes angiotensin-converting enzyme inhibitors and β -adrenergic blocking agents used for other causes of heart failure, with careful suppression of “inappropriate” sinus tachycardia, and attention to postural hypotension that can occur in these patients. Once

thought to have an inexorable downward course, some patients with doxorubicin cardiotoxicity improve under careful management to near-normal clinical function for many years.

Trastuzumab (Herceptin) is a monoclonal antibody that interferes with cell surface receptors crucial for some tumor growth and for cardiac adaptation. The incidence of cardiotoxicity is lower than for anthracyclines but enhanced by coadministration with them. Although considered to be more often reversible, trastuzumab cardiotoxicity does not always resolve, and some patients progress to clinical heart failure and death. As with anthracycline cardiotoxicity, therapy is as usual for heart failure, but it is not clear whether the spontaneous rate of improvement is enhanced by neurohormonal antagonists.

Cardiotoxicity with cyclophosphamide and ifosfamide generally occurs acutely and with very high doses. 5-Fluorouracil, cisplatin, and some other alkylating agents can cause recurrent coronary spasm that occasionally leads to depressed contractility. Acute administration of interferon- α can cause hypotension and arrhythmias. Clinical heart failure occurring during repeated chronic administration usually resolves after discontinuation.

Many small-molecule tyrosine kinase inhibitors are under development for different malignancies. Although these agents are “targeted” at specific tumor receptors or pathways, the biologic conservation of signaling pathways can cause these inhibitors to have “off-target” effects that include the heart and vasculature. Recognition of cardiotoxicity during therapy with these agents is complicated because they occasionally cause peripheral fluid accumulation (ankle edema, periorbital swelling, pleural effusions) due to local factors rather than elevated central venous pressures. Therapeutic approaches include withdrawal of the tyrosine kinase inhibitor (when possible) and substitution with a congener (when available), as well as conventional treatment for heart failure. Prophylactic treatment with beta blockers and angiotensin-converting enzyme inhibitors prior to and during chemotherapy is a topic of ongoing investigation.

Other therapeutic drugs that can cause cardiotoxicity during chronic use include hydroxychloroquine, chloroquine, emetine, and antiretroviral therapies.

Toxic exposures can cause arrhythmias or respiratory injury acutely during accidents. Chronic exposures implicated in cardiotoxicity include hydrocarbons, fluorocarbons, arsenicals, lead, and mercury.

METABOLIC CAUSES OF CARDIOMYOPATHY

Endocrine disorders affect multiple organ systems, including the heart. Hyperthyroidism and hypothyroidism do not often cause clinical heart failure in an

otherwise normal heart, but commonly exacerbate heart failure. Clinical signs of thyroid disease may be masked, so tests of thyroid function are part of the routine evaluation of cardiomyopathy. Hyperthyroidism should always be considered with new-onset atrial fibrillation or ventricular tachycardia or atrial fibrillation in which the rapid ventricular response is difficult to control. The most common current reason for thyroid abnormalities in the cardiac population is the treatment of tachyarrhythmias with amiodarone, a drug with substantial iodine content. Hypothyroidism should be treated with very slow escalation of thyroid supplements to avoid exacerbating tachyarrhythmias and heart failure. Hyperthyroidism and heart failure are a dangerous combination that merits very close supervision, often hospitalization, during titration of antithyroid medications, during which decompensation of heart failure may occur precipitously and fatally.

Pheochromocytoma is rare, but should be considered when a patient has heart failure and very labile blood pressure and heart rate, sometimes with episodic palpitations. Patients with pheochromocytoma often have postural hypotension. In addition to α -adrenergic receptor antagonists, definitive therapy requires surgical extirpation. Very high renin states, such as those caused by renal artery stenosis, can lead to modest depression in ejection fraction with little or no ventricular dilation and markedly labile symptoms with flash pulmonary edema, related to sudden shifts in vascular tone and intravascular volume.

Controversies remain regarding whether diabetes and obesity are sufficient to cause cardiomyopathy. Most heart failure in diabetes results from epicardial coronary disease, with further increase in coronary artery risk due to accompanying hypertension and renal dysfunction. Cardiomyopathy may result in part from insulin resistance and increased advanced-glycosylation end products, which impair both systolic and diastolic function. However, much of the dysfunction can be attributed to scattered focal ischemia resulting from distal coronary artery tapering and limited microvascular perfusion even without proximal focal stenoses. Diabetes is a typical factor in heart failure with “preserved” ejection fraction, along with hypertension, advanced age, and female gender.

The existence of a cardiomyopathy due to obesity is generally accepted. In addition to cardiac involvement from associated diabetes, hypertension, and vascular inflammation of the metabolic syndrome, obesity alone is associated with impaired excretion of excess volume load, which, over time, can lead to increased wall stress and secondary adaptive neurohumoral responses. Fluid retention may be aggravated by large fluid intake and the rapid clearance of natriuretic

peptides by adipose tissue. In the absence of another obvious cause of cardiomyopathy in an obese patient with systolic dysfunction without marked ventricular dilation, effective weight reduction is often associated with major improvement in ejection fraction and clinical function. Improvement in cardiac function has been described after successful bariatric surgery, although all major surgical therapy poses increased risk for patients with heart failure. Postoperative malabsorption and nutritional deficiencies, such as calcium and phosphate deficiencies, may be particularly deleterious for patients with cardiomyopathy.

Nutritional deficiencies can occasionally cause dilated cardiomyopathy but are not commonly implicated in developed Western countries. Beri-beri heart disease due to thiamine deficiency can result from poor nutrition in undernourished populations and in patients deriving most of their calories from alcohol, and has been reported in teenagers subsisting only on highly processed foods. This disease is initially a vasodilated state with very high output heart failure that can later progress to a low output state; thiamine repletion can lead to prompt recovery of cardiovascular function. Abnormalities in carnitine metabolism can cause dilated or restrictive cardiomyopathies, usually in children. Deficiency of trace elements such as selenium can cause cardiomyopathy (Keshan’s disease).

Calcium is essential for excitation-contraction coupling. Chronic deficiencies of calcium, such as can occur with hypoparathyroidism (particularly postsurgical) or intestinal dysfunction (from diarrheal syndromes and following extensive resection), can cause severe chronic heart failure that responds over days or weeks to vigorous calcium repletion. Phosphate is a component of high-energy compounds needed for efficient energy transfer and multiple signaling pathways. Hypophosphatemia can develop during starvation and early refeeding following a prolonged fast, and occasionally during hyperalimentation. Magnesium is a cofactor for thiamine-dependent reactions and for the sodium-potassium adenosine triphosphatase (ATPase), but hypomagnesemia rarely becomes sufficiently profound to cause clinical cardiomyopathy.

Hemochromatosis is variably classified as a metabolic or storage disease. It is included among the causes of restrictive cardiomyopathy, but the clinical presentation is often that of a dilated cardiomyopathy. The autosomal recessive form is related to the HFE gene. With up to 10% of the population heterozygous for one mutation, the clinical prevalence might be as high as 1 in 500. The lower observed rates highlight the limited penetrance of the disease, suggesting the role of additional genetic and environmental factors for clinical expression. Hemochromatosis can also be acquired from iron overload due to hemolytic anemia and transfusions. Excess iron is

deposited in the perinuclear compartment of cardiomyocytes, with resulting disruption of intracellular architecture and mitochondrial function. Diagnosis is easily made from measurement of serum iron and transferrin saturation, with a threshold of >60% for men and >45–50% for women. MRI can help to quantitate iron stores in the liver and heart, and endomyocardial biopsy tissue can be stained for iron (**Fig. 27-9**), which is particularly important if the patient has another cause for cardiomyopathy. If diagnosed early, hemochromatosis can often be managed by repeated phlebotomy to remove iron. For more severe iron overload, iron chelation therapy with desferrioxamine (deferrioxamine) or deferasirox can help to improve cardiac function if myocyte loss and replacement fibrosis are not too severe.

Inborn disorders of metabolism occasionally present with dilated cardiomyopathy, although they are most often associated with restrictive cardiomyopathy (Table 27-4).

FAMILIAL DILATED CARDIOMYOPATHY

The genetic basis for cardiomyopathy is discussed in the section, “Genetic Etiologies of Cardiomyopathy.” The recognized frequency of familial involvement in dilated cardiomyopathy has increased to over 30%. Mutations in TTN, encoding the giant sarcomeric protein titin, are the most common cause of dilated cardiomyopathy, accounting for up to 25% of familial disease. On average, men with TTN mutations develop cardiomyopathy a decade before women, without distinctive clinical features. Mutations in thick and thin filament genes account for ~8% of dilated cardiomyopathy and may manifest in early childhood.

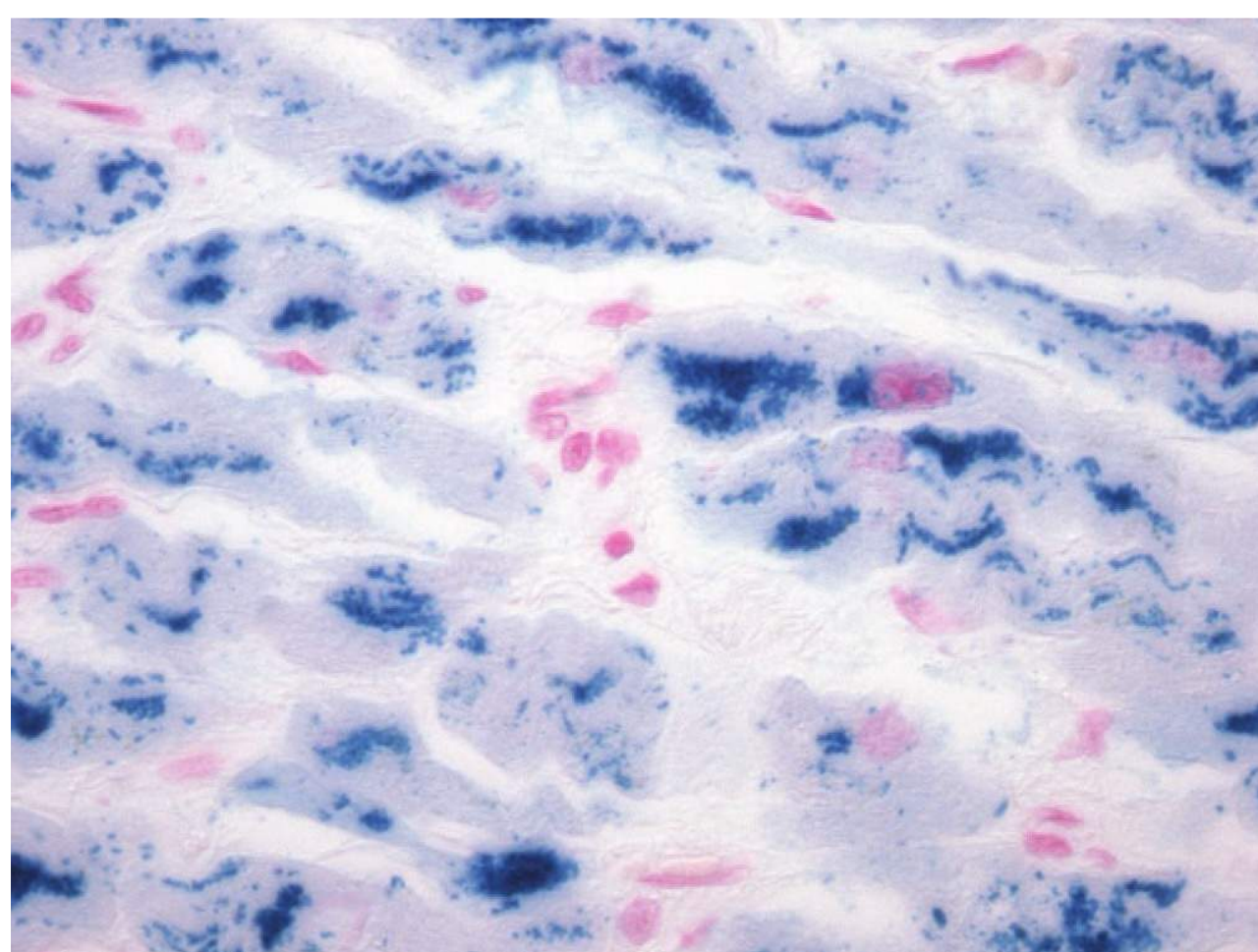


FIGURE 27-9

Hemochromatosis. Microscopic image of an endomyocardial biopsy showing extensive iron deposition within the cardiac myocytes with the Prussian blue stain (400× original magnification). (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women’s Hospital, Boston.)

The most recognizable familial cardiomyopathy syndromes with extracardiac manifestations are the muscular dystrophies. Both Duchenne’s and the milder Becker’s dystrophy result from abnormalities in the X-linked dystrophin gene of the sarcolemmal membrane. Skeletal myopathy is present in multiple other genetic cardiomyopathies (Table 27-3), some of which are associated with creatine kinase elevations.

Families with a history of atrial arrhythmias, conduction system disease, and cardiomyopathy may have abnormalities of the nuclear membrane lamin proteins. While all dilated cardiomyopathies carry a risk of sudden death, a family history of cardiomyopathy with sudden death raises suspicion for a particularly arrhythmogenic mutation; affected family members may be considered for implantable defibrillators even before meeting the reduced ejection fraction threshold for primary prevention of sudden death.

A prominent family history of sudden death or ventricular tachycardia before clinical cardiomyopathy suggests genetic defects in the desmosomal proteins (**Fig. 27-10**). Originally described as affecting the right ventricle (arrhythmogenic right ventricular dysplasia [ARVD]), this disorder (arrhythmogenic ventricular dysplasia) can affect either or both ventricles. Patients often present first with ventricular tachycardia. Genetic defects in proteins of the desmosomal complex disrupt myocyte junctions and adhesions, leading to replacement of myocardium by deposits of fat. Thin ventricular walls may be recognized on echocardiography but are better visualized on MRI. Because desmosomes are also important for elasticity of hair and skin, some of the defective desmosomal proteins are associated with striking “woolly hair” and thickened skin on the palms and soles. Implantable defibrillators are usually indicated to prevent sudden death. There is variable progression to right, left, or biventricular failure.

Left ventricular noncompaction is a condition of unknown prevalence that is increasingly revealed with the refinement of imaging techniques. The diagnostic criteria include the presence of multiple trabeculations in the left ventricle distal to the papillary muscles, creating a “spongy” appearance of the apex. Noncompaction has been associated with multiple genetic variants in the sarcomeric and other genes, such as TAZ (encoding tafazzin). The diagnosis may be made incidentally or in patients previously diagnosed with cardiomyopathy, in whom the criteria for noncompaction may appear and resolve with changing left ventricular size and function. The three cardinal clinical features are ventricular arrhythmias, embolic events, and heart failure. Treatment generally includes anticoagulation and early consideration for an implantable defibrillator, in addition to neurohormonal antagonists as indicated by stage of disease.

Some families inherit a susceptibility to viral-induced myocarditis. This propensity may relate to abnormalities

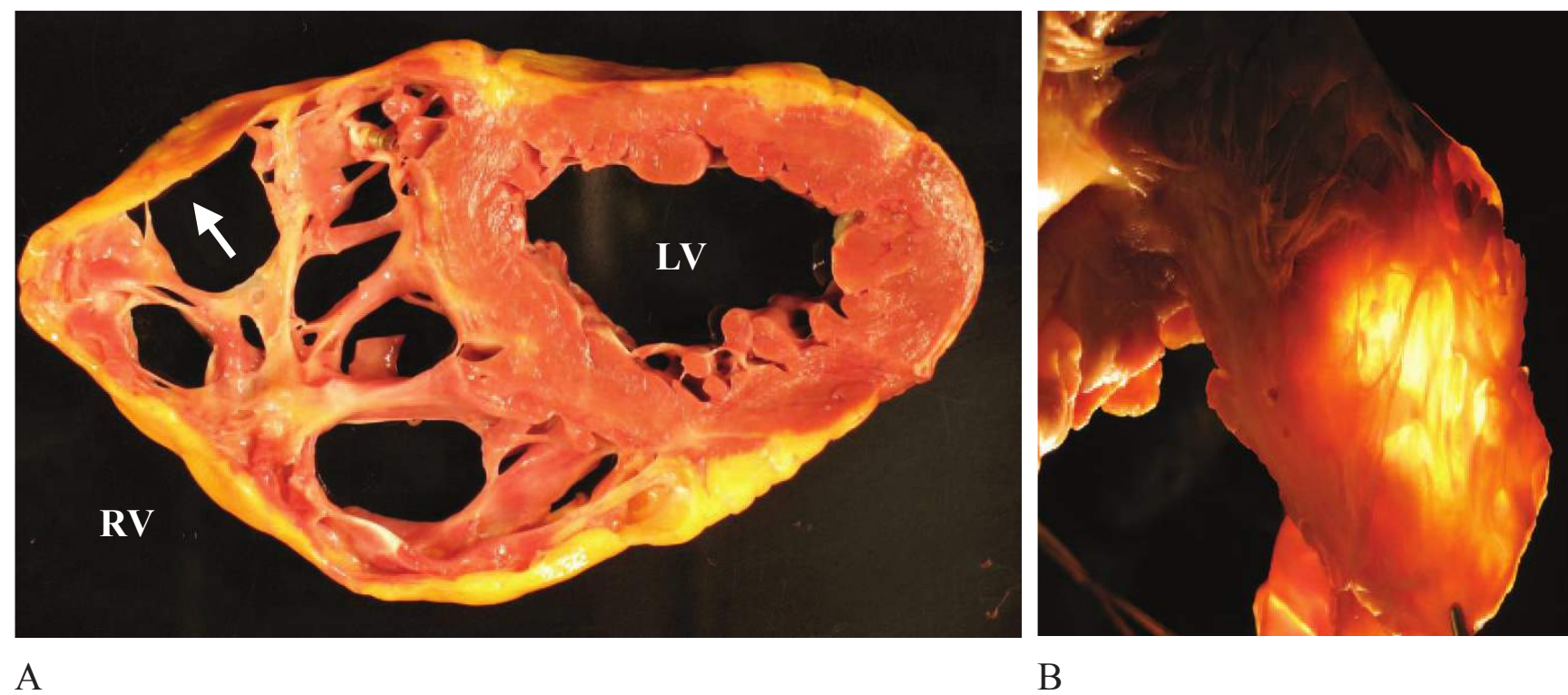


FIGURE 27-10

Arrhythmogenic right ventricular dysplasia. A. Cross-sectional slice of a pathology specimen removed at transplantation, showing severe dysplasia of the right ventricle (RV) with extensive fatty replacement of right ventricular myocardium. B. The remarkably

thin right ventricular free wall is revealed by transillumination. LV, left ventricle. (Images courtesy of Gayle Winters, MD, and Richard Mitchell, MD, PhD, Division of Pathology, Brigham and Women's Hospital, Boston.)

in cell surface receptors, such as the coxsackie-adenovirus receptor, that bind viral proteins. Some may have partial homology with viral proteins such that an autoimmune response is triggered against the myocardium.

Prognosis and therapy of familial dilated cardiomyopathy are dictated primarily by the stage of clinical disease and the risk for sudden death. In some cases, the familial etiology facilitates prognostic decisions, particularly regarding the likelihood of recovery after a new diagnosis, which is unlikely for familial disease. The rate of progression of disease, once manifest, is, to some extent, heritable, although marked variation can be seen. However, there have been cases of remarkable clinical remission after acute presentation, likely after a reversible additional insult, such as prolonged tachycardia or infective myocarditis.

TAKOTSUBO CARDIOMYOPATHY

The apical ballooning syndrome, or stress-induced cardiomyopathy, occurs typically in older women after sudden intense emotional or physical stress. The ventricle shows global ventricular dilation with basal contraction, forming the shape of the narrow-necked jar (takotsubo) used in Japan to trap octopi. Originally described in Japan, it is increasingly recognized elsewhere during emergency cardiac catheterization and intensive care unit admissions for noncardiac conditions. Presentations include pulmonary edema, hypotension, and chest pain with ECG changes mimicking an acute infarction. The left ventricular dysfunction extends beyond a specific coronary artery distribution and generally resolves within days to weeks. Animal models and ventricular biopsies suggest that this acute cardiomyopathy may result from intense sympathetic activation with heterogeneity of myocardial autonomic innervation, diffuse microvascular spasm, and/or direct catecholamine

toxicity. Coronary angiography may be required to rule out acute coronary occlusion. No therapies have been proven beneficial, but reasonable strategies include nitrates for pulmonary edema, intraaortic balloon pump if needed for low output, combined alpha and beta blockers rather than selective beta blockade if hemodynamically stable, and magnesium for arrhythmias related to QT prolongation. Anticoagulation is generally withheld due to the occasional occurrence of ventricular rupture. While the prognosis is generally good, recurrences have been described in up to 10% of patients.

IDIOPATHIC DILATED CARDIOMYOPATHY

Idiopathic dilated cardiomyopathy is a diagnosis of exclusion, when all other known factors have been excluded. Approximately two-thirds of dilated cardiomyopathies are still labeled as idiopathic; however, a substantial proportion of these may reflect unrecognized genetic disease. Continued reconsideration of etiology during chronic heart failure management often reveals specific causes later in a patient's course.

OVERLAPPING TYPES OF CARDIOMYOPATHY

The limitations of our phenotypic classification are revealed through the multiple overlaps between the etiologies and presentations of the three types. Cardiomyopathy with reduced systolic function but without severe dilation can represent early dilated cardiomyopathy, "minimally dilated cardiomyopathy," or restrictive diseases without marked increases in ventricular wall thickness. For example, sarcoidosis and hemochromatosis can present as dilated or restrictive disease. Early stages of amyloidosis are often mistaken for hypertrophic cardiomyopathy. Progression of hypertrophic

cardiomyopathy into a “burned-out” phase occurs occasionally, with decreased contractility and modest ventricular dilation. Overlaps are particularly common with the inherited metabolic disorders, which can present as any of the three major phenotypes (Fig. 27-4).

DISORDERS OF METABOLIC PATHWAYS

Multiple genetic disorders of metabolic pathways can cause myocardial disease, due to infiltration of abnormal products or cells containing them between the myocytes, and storage disease, due to their accumulation within cells (see [Table 27-5](#)). The restrictive phenotype is most common, but mildly dilated cardiomyopathy may occur. Hypertrophic cardiomyopathy may be mimicked by the myocardium thickened with these abnormal products causing “pseudohypertrophy.” Most of these diseases are diagnosed during childhood.

Fabry’s disease results from a deficiency of the lysosomal enzyme alpha-galactosidase A caused by one of more than 160 mutations. This disorder of glycosphingolipid metabolism is an X-linked recessive disorder that may also cause clinical disease in female carriers. Glycolipid accumulation may be limited to the cardiac tissues or may also involve the skin and kidney. Electron microscopy of endomyocardial biopsy tissue shows diagnostic vesicles containing concentric lamellar figures ([Fig. 27-11](#)). Diagnosis is crucial because enzyme replacement can reduce abnormal deposits and improve cardiac and clinical function. The magnitude of clinical impact has not been well-established for this therapy, which requires frequent infusions of the enzyme at a cost of over \$100,000 a year. Enzyme replacement can also improve the course of Gaucher’s disease, in which cerebroside-rich cells accumulate in multiple organs due to a deficiency of beta-glucosidase. Cerebroside-rich cells infiltrate the heart, which can also lead to a hemorrhagic pericardial effusion and valvular disease.

Glycogen storage diseases lead to accumulation of lysosomal storage products and intracellular glycogen accumulation, particularly with glycogen storage disease type III, due to a defective debranching enzyme. There are more than 10 types of mucopolysaccharidoses, in which autosomal dominant or X-linked deficiencies of lysosomal enzymes lead to the accumulation of glycosaminoglycans in the skeleton, nervous system, and occasionally the heart. With characteristic facies, short stature, and frequent cognitive impairment, most individuals are diagnosed early in childhood and die before adulthood.

Carnitine is an essential cofactor in long-chain fatty acid metabolism. Multiple defects have been described that lead to carnitine deficiency, causing

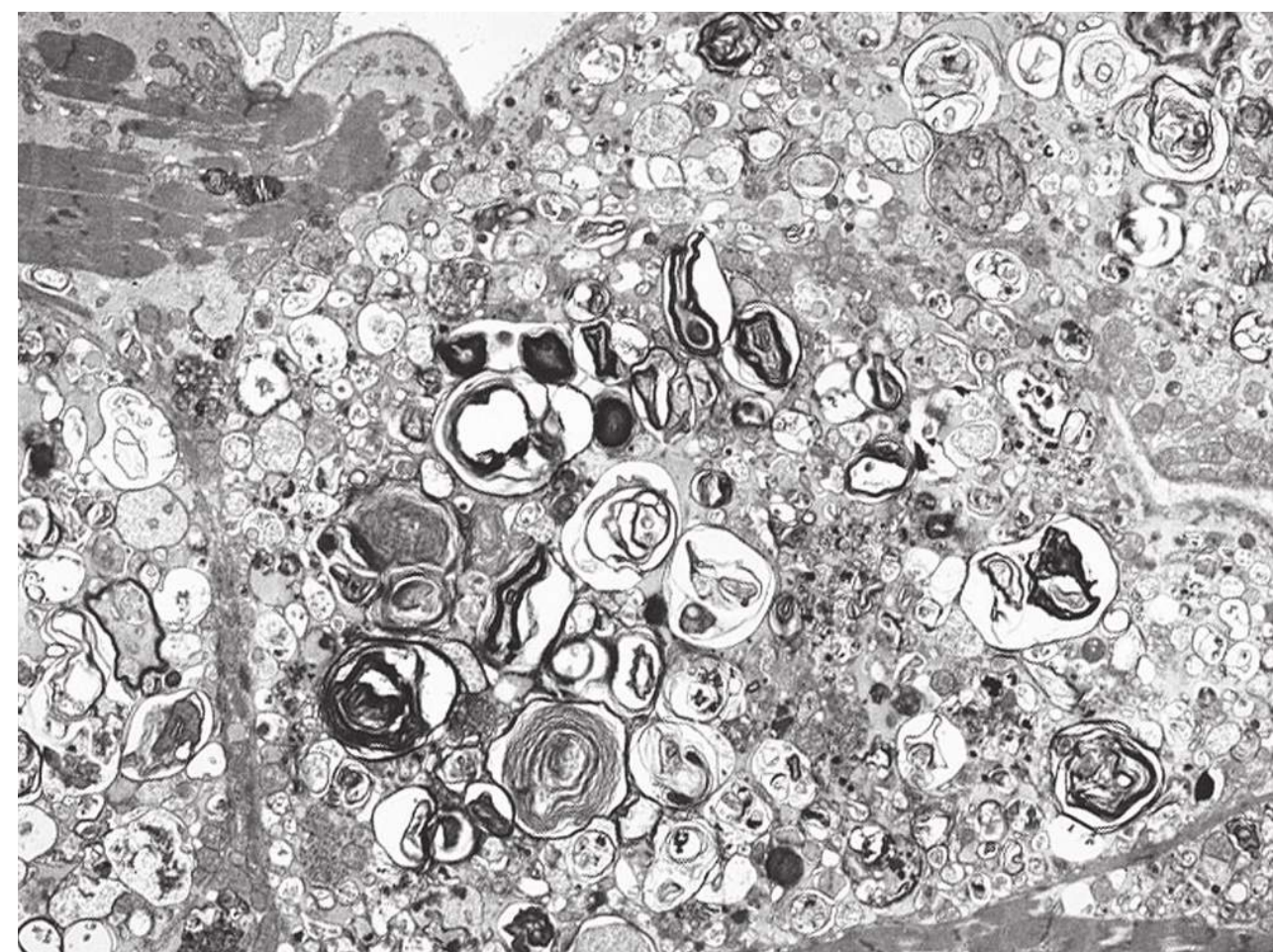


FIGURE 27-11

Fabry’s disease. Transmission electron micrograph of a right ventricular endomyocardial biopsy specimen at high magnification showing the characteristic concentric lamellar inclusions of glycosphingolipids accumulating as a result of deficiency of the lysosomal enzyme alpha-galactosidase A. Image taken at 15,000 $\times$ original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women’s Hospital, Boston.)

intracellular lipid inclusions and restrictive or dilated cardiomyopathy, often presenting in children. Fatty acid oxidation requires many metabolic steps with specific enzymes that can be deficient, with complex interactions with carnitine. Depending on the defect, cardiac and skeletal myopathy can be ameliorated with replacement of fatty acid intermediates and carnitine.

Two monogenic metabolic cardiomyopathies have recently been described as causes of increased ventricular wall thickness without an increase of muscle subunits or an increase in contractility. Mutations in the gamma-2 regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase important for glucose metabolism (PRKAG2) have been associated with a high prevalence of conduction abnormalities, such as AV block and ventricular preexcitation (Wolff-Parkinson-White syndrome). Several defects have been reported in an X-linked lysosome-associated membrane protein (LAMP2). This defect can be maternally transmitted or sporadic and has occasionally been isolated to the heart, although it often leads to a syndrome of skeletal myopathy, mental retardation, and hepatic dysfunction referred to as Danon’s disease. Extreme left ventricular hypertrophy appears early, often in childhood, and can progress rapidly to end-stage heart failure with low ejection fraction. Electron microscopy of these metabolic disorders shows that the myocytes are enlarged by multiple intracellular vacuoles of metabolic by-products.

The least common of the physiologic triad of cardiomyopathies is restrictive cardiomyopathy, which is dominated by abnormal diastolic function, often with mildly decreased contractility and ejection fraction (usually >30–50%). Both atria are enlarged, sometimes massively. Modest left ventricular dilation can be present, usually with an end-diastolic dimension <6 cm. End-diastolic pressures are elevated in both ventricles, with preservation of cardiac output until late in the disease. Subtle exercise intolerance is usually the first symptom but is often not recognized until after clinical presentation with congestive symptoms. The restrictive diseases often present with relatively more right-sided symptoms, such as edema, abdominal discomfort, and ascites, although filling pressures are elevated in both ventricles. The cardiac impulse is less displaced than in dilated cardiomyopathy and less dynamic than in hypertrophic cardiomyopathy. A fourth heart sound is more common than a third heart sound in sinus rhythm, but atrial fibrillation is common. Jugular venous pressures often show rapid Y descents and may increase during inspiration (positive Kussmaul’s sign). Most restrictive cardiomyopathies are due to infiltration of abnormal substances between myocytes, storage of abnormal metabolic products within myocytes, or fibrotic injury (Table 27-5). The differential diagnosis should include constrictive pericardial disease, which may also be dominated by right-sided heart failure.

INFILTRATIVE DISEASE

Amyloidosis is the major cause of restrictive cardiomyopathy (Figs. 27-12, 27-13, 27-14). Several proteins can self-assemble to form the beta-sheets of amyloid proteins, which deposit with different consequences depending on the type of protein. In addition to cardiac infiltration, neurologic involvement occurs commonly with primary amyloidosis (immunoglobulin light chains) and with familial amyloidosis (genetic abnormalities of transthyretin). There are over 100 identified mutations in transthyretin on chromosome 13, among which the V122I transthyretin mutation has been identified in about 4% of African Americans and in 10% of African Americans with heart failure and may contribute importantly to heart failure in general in the elderly African-American population. Organ dysfunction was previously attributed solely to physical disruption from the infiltrating amyloid fibrils, but newer information suggests additional direct toxicity from the immunoglobulin light chain and abnormal transthyretin protein aggregates themselves. In senile amyloidosis, there is abnormal accumulation of normal transthyretin or

TABLE 27-5
CAUSES OF RESTRICTIVE CARDIOMYOPATHIES

Infiltrative (Between Myocytes)
Amyloidosis
Primary (light chain amyloid)
Familial (abnormal transthyretin) ^a
Senile (normal transthyretin or atrial peptides)
Inherited metabolic defects ^a
Storage (Within Myocytes)
Hemochromatosis (iron) ^a
Inherited metabolic defects ^a
Fabry’s disease
Glycogen storage disease (II, III)
Fibrotic
Radiation
Scleroderma
Endomyocardial
Possibly related fibrotic diseases
Tropical endomyocardial fibrosis
Hypereosinophilic syndrome (Löf er’s endocarditis)
Carcinoid syndrome
Radiation
Drugs: e.g., serotonin, ergotamine
Overlap with Other Cardiomyopathies
Hypertrophic cardiomyopathy/”pseudohypertrophic” ^a
“Minimally dilated”cardiomyopathy
Early-stage dilated cardiomyopathy
Partial recovery from dilated cardiomyopathy
Sarcoidosis
Idiopathic ^a

^aCan be familial.

natriuretic peptide folding, detected in 10% of people over 80 years and half of those over 90 years but often without apparent clinical disease. Men show a greater burden of amyloid deposition and 20-fold greater likelihood of clinical disease with senile amyloidosis. The aging of the population will soon render senile amyloidosis the most common of the amyloidoses.

Cardiac amyloid is classically suspected from thickened ventricular walls with an ECG that shows low voltage. However, low voltage is not always present and is less common in familial or senile amyloidosis than in primary AL amyloidosis. A characteristic refractile brightness in the septum on echocardiography is suggestive of the diagnosis, but neither sensitive nor specific. Both atria are dilated, often dramatically, and diastolic dysfunction may be more obvious than in left ventricular hypertrophy from other causes. Amyloid infiltration can also be detected with gadolinium enhancement in MRI. The diagnosis of primary or familial amyloidosis can sometimes be made from biopsies of an abdominal fat pad or the rectum, but cardiac



FIGURE 27-12

Restrictive cardiomyopathy—amyloidosis. Gross specimen of a heart with amyloidosis. The heart is firm and rubbery with a waxy cut surface. The atria are markedly dilated, and the left atrial endocardium, normally smooth, has yellow-brown amyloid deposits that give texture to the surface. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

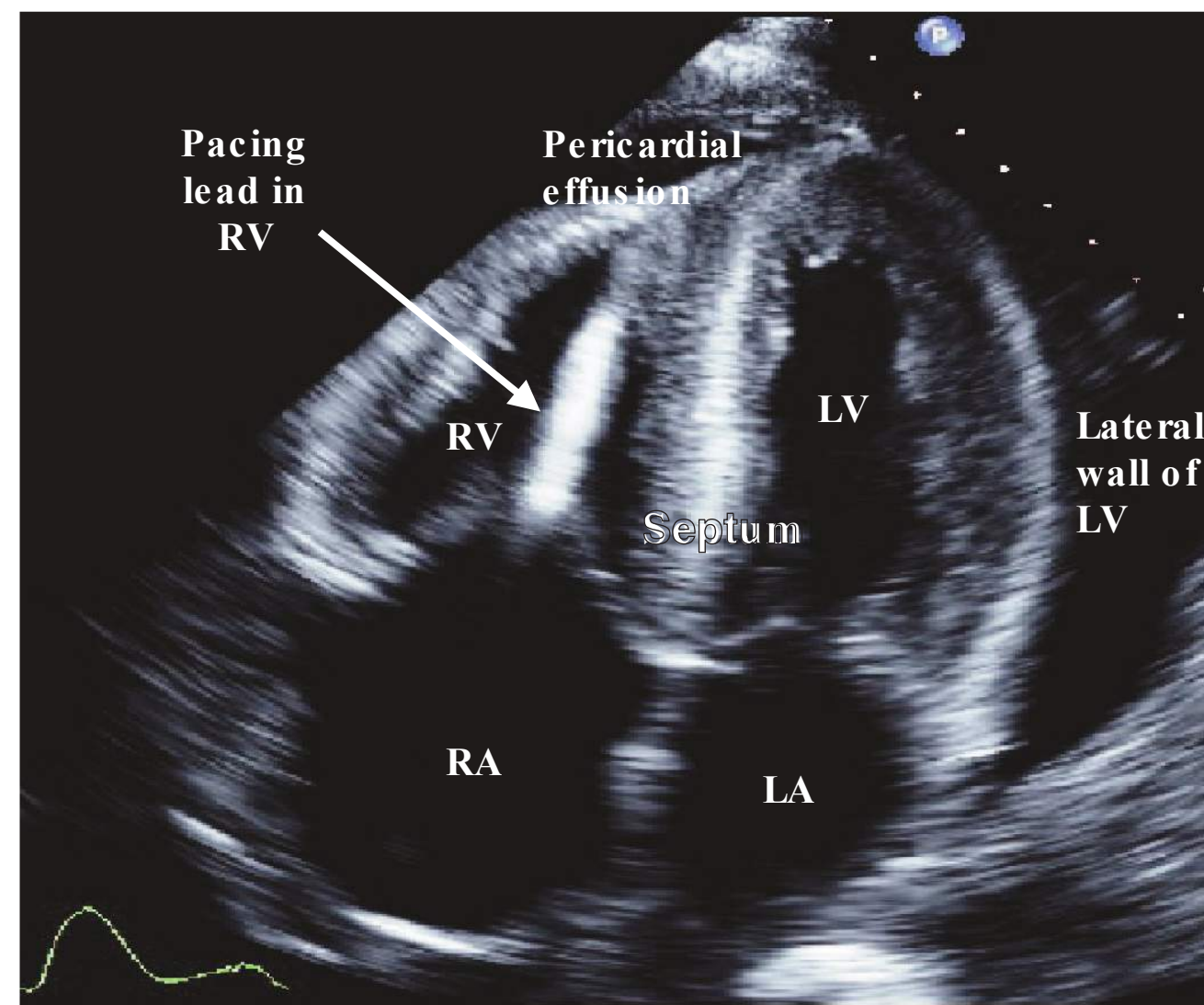


FIGURE 27-13

Restrictive cardiomyopathy—amyloidosis. Echocardiogram showing thickened walls of both ventricles without major chamber dilation. The atria are markedly dilated, consistent with chronically elevated ventricular filling pressures. In this example, there is a characteristic hyperrefractile "glittering" of the myocardium typical of amyloid infiltration, which is often absent (especially with more recent echocardiographic systems of better resolution). The mitral and tricuspid valves are thickened. A pacing lead is visible in the right ventricle (RV), and a pericardial effusion is evident. Note that the echocardiographic and pathologic images are vertically opposite, such that the left ventricle (LV) is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. LA, left atrium; RA, right atrium. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

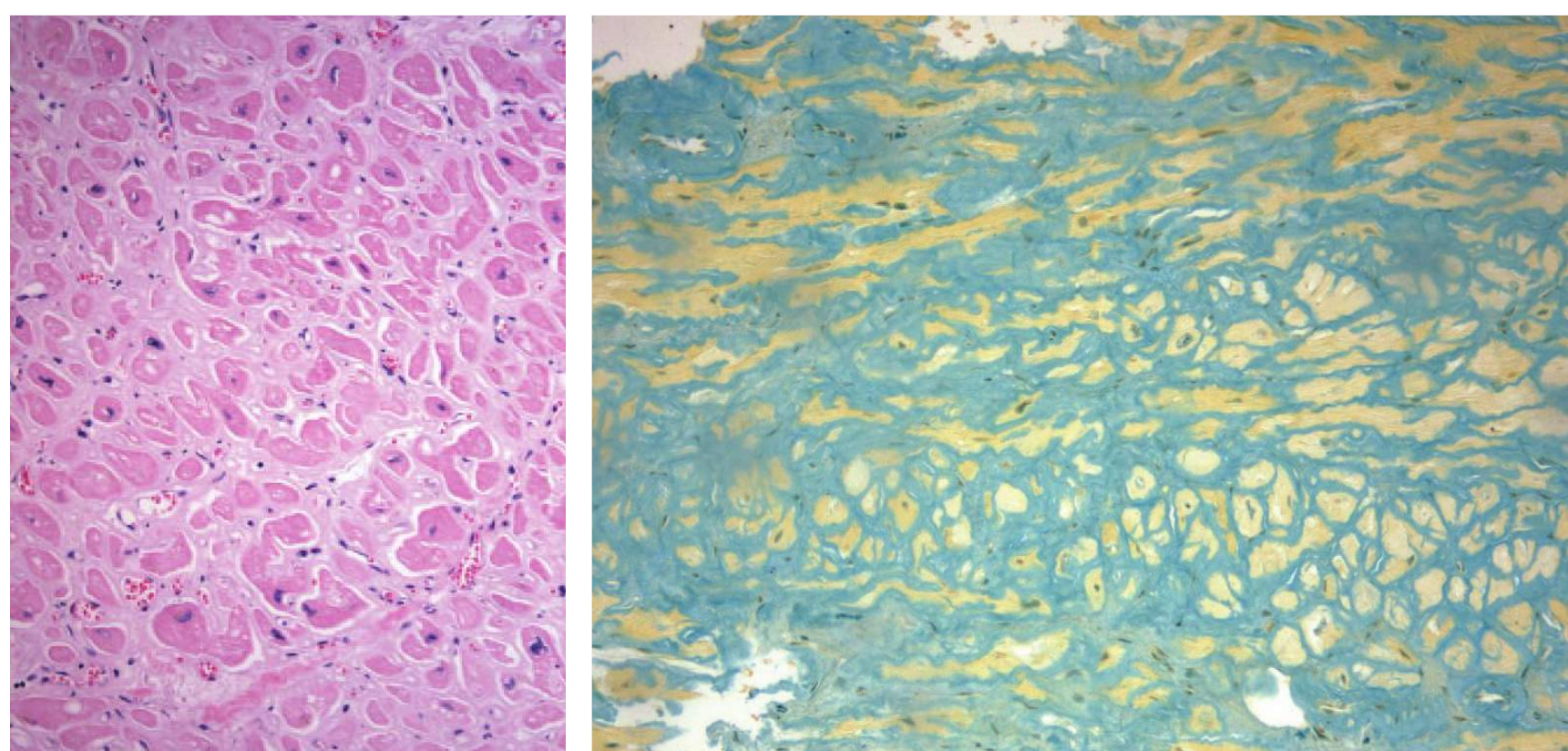


FIGURE 27-14

Amyloidosis—microscopic images of amyloid involving the myocardium. The left panel (hematoxylin and eosin stain) shows glassy, grey-pink amorphous material infiltrating between cardiomyocytes, which stain a darker pink. The right panel shows a sulfated blue stain that highlights the amyloid green and stains the cardiac myocytes yellow. (The Congo red stain can also be

used to highlight amyloid; under polarized light, amyloid will have an apple-green birefringence when stained with Congo red.) Images at 100× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

amyloidosis is most reliably identified from a biopsy of the heart, in which amyloid fibrils infiltrate the myocardium diffusely, particularly around the conduction system and coronary vessels (Fig. 27-14). Diagnosis of the type of amyloid protein requires immunohistochemistry of biopsied tissue rather than serum or urine electrophoresis, which can lead to incorrect classification.

Therapy for all types of amyloid is predominantly for symptoms of fluid retention, which often requires high doses of loop diuretics. Digoxin bound to the amyloid fibrils can reach toxic levels, and should therefore be used only in very low doses, if at all. There is no evidence regarding use of neurohormonal antagonists in amyloid heart disease, where the possible theoretical benefit has to be balanced against the possibility of aggravating postural hypotension and diminishing the crucial heart rate reserve. The risk of intracardiac thrombi may warrant chronic anticoagulation.

The prognosis is worst for primary amyloid, with a median survival of 6–12 months after symptoms of heart failure. If present, multiple myeloma is treated with chemotherapy, the extent of which is often limited by the potential of worsening cardiac dysfunction. Immunoglobulin-associated amyloid has occasionally been treated with sequential heart transplantation and delayed bone marrow transplant, with frequent recurrence of amyloid in the transplanted heart. Abnormal transthyretin-associated cardiac amyloid has a somewhat better prognosis and can be treated in selected patients with heart and liver transplantation. Senile cardiac amyloid has the slowest progression and best overall prognosis.

FIBROTIC RESTRICTIVE CARDIOMYOPATHY

Progressive fibrosis can cause restrictive myocardial disease without ventricular dilation. Thoracic radiation, common for breast and lung cancer or mediastinal lymphoma, can produce early or late restrictive cardiomyopathy. Patients with radiation cardiomyopathy may present with a possible diagnosis of constrictive pericarditis, as the two conditions often coexist. Careful hemodynamic evaluation and, often, endomyocardial biopsy should be performed if considering pericardial stripping surgery, which is unlikely to be successful in the presence of underlying restrictive cardiomyopathy.

Scleroderma causes small vessel spasm and ischemia that can lead to a small, stiff heart with reduced ejection fraction without dilation. The pulmonary hypertension associated with scleroderma may lead to more clinical right heart failure because of concomitant fibrotic disease of the right ventricle. Doxorubicin causes direct myocyte injury usually leading to dilated cardiomyopathy, but the limited degree of dilation may result from increased fibrosis, which restricts remodeling.

ENDOMYOCARDIAL DISEASE

The physiologic picture of elevated filling pressures with atrial enlargement and preserved ventricular contractility with normal or reduced ventricular volumes can result from extensive fibrosis of the endocardium, without transmural myocardial disease. For patients who have not lived in the equatorial regions, this picture is rare, and when seen is often associated with a history of chronic hypereosinophilic syndrome (Löf er's endocarditis), which is more common in men than women. In this disease, persistent hypereosinophilia of >1500 eos/mm³ for at least 6 months can cause an acute phase of eosinophilic injury in the endocardium (see earlier discussion of eosinophilic myocarditis), with systemic illness and injury to other organs. There is usually no obvious cause, but the hypereosinophilia can occasionally be explained by allergic, parasitic, or malignant disease. It is postulated to be followed by a period in which cardiac inflammation is replaced by evidence of fibrosis with superimposed thrombosis. In severe disease, the dense fibrotic layer can obliterate the ventricular apices and extend to thicken and tether the AV valve leaflets. The clinical disease may present with heart failure, embolic events, and atrial arrhythmias. While plausible, the sequence of transition from eosinophilic myocarditis or Löf er's endocarditis to endomyocardial fibrosis has not been clearly demonstrated.

In tropical countries, up to one-quarter of heart failure may be due to endomyocardial fibrosis, affecting either or both ventricles. This condition shares with the previous condition the partial obliteration of the ventricular apex with fibrosis extending into the valvular inflow tract and leaflets; however, it is not clear that the etiologies are the same for all cases. Pericardial effusions frequently accompany endomyocardial fibrosis but are not common in Löf er's endocarditis. For endomyocardial fibrosis, there is no gender difference, but a higher prevalence in African-American populations. While tropical endomyocardial fibrosis could represent the end-stage of previous hypereosinophilic disease triggered by endemic parasites, neither prior parasitic infection nor hypereosinophilia is usually documented. Geographic nutritional deficiencies have also been proposed as an etiology.

Medical treatment focuses on glucocorticoids and chemotherapy to suppress hypereosinophilia when present. Fluid retention may become increasingly resistant to diuretic therapy. Anticoagulation is recommended. Atrial fibrillation is associated with worse symptoms and prognosis, but may be difficult to suppress. Surgical resection of the apices and replacement of the fibrotic valves can improve symptoms, but surgical morbidity and mortality and later recurrence rates are high.

The serotonin secreted by carcinoid tumors can produce fibrous plaques in the endocardium and right-sided cardiac valves, occasionally affecting left-sided

valves, as well. Valvular lesions may be stenotic or regurgitant. Systemic symptoms include flushing and diarrhea. Liver disease from hepatic metastases may play a role by limiting hepatic function and thereby allowing more serotonin to reach the venous circulation.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is defined as left ventricular hypertrophy that develops in the absence of causative hemodynamic factors, such as hypertension, aortic valve disease, or systemic infiltrative or storage diseases (Figs. 27-15 and 27-16). It has previously been termed hypertrophic obstructive cardiomyopathy (HOCM), asymmetric septal hypertrophy (ASH), and idiopathic hypertrophic subaortic stenosis (IHSS). However, the accepted terminology is now hypertrophic cardiomyopathy with or without obstruction. Prevalence in North America, Japan, and China is about 1:500. It is the leading cause of sudden death in the young and is an important cause of heart failure. Although pediatric presentation is associated with increased early

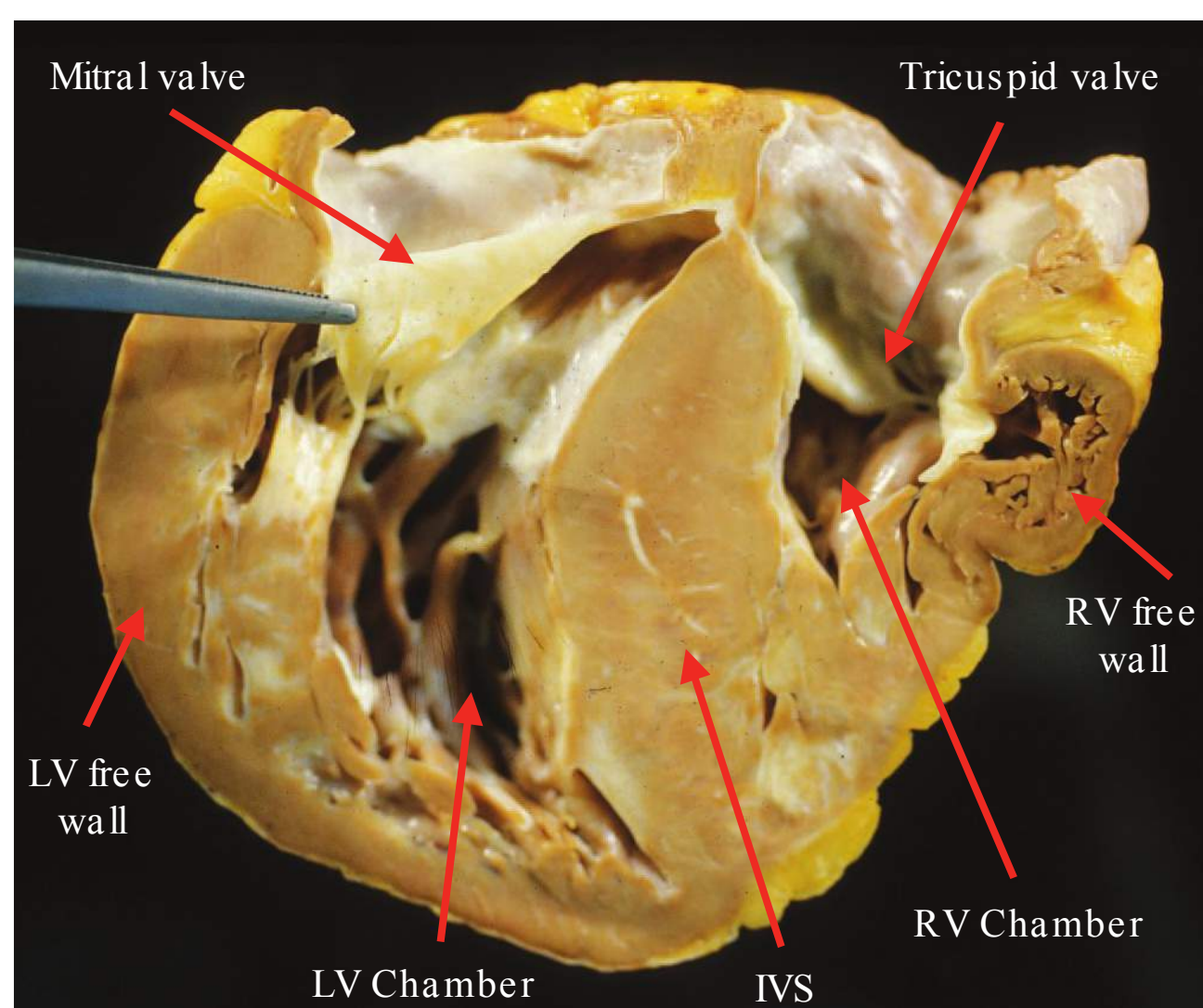


FIGURE 27-15

Hypertrophic cardiomyopathy. Gross specimen of a heart with hypertrophic cardiomyopathy removed at the time of transplantation, showing asymmetric septal hypertrophy (septum much thicker than left ventricular free wall) with the septum bulging into the left ventricular outflow tract causing obstruction. The forceps are retracting the anterior leaflet of the mitral valve, demonstrating the characteristic plaque of systolic anterior motion, manifest as endocardial fibrosis on the interventricular septum in a mirror-image pattern to the valve leaflet. There is patchy replacement fibrosis, and small thick-walled arterioles can be appreciated grossly, especially in the interventricular septum. IVS, interventricular septum; LV, left ventricle; RV, right ventricle. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

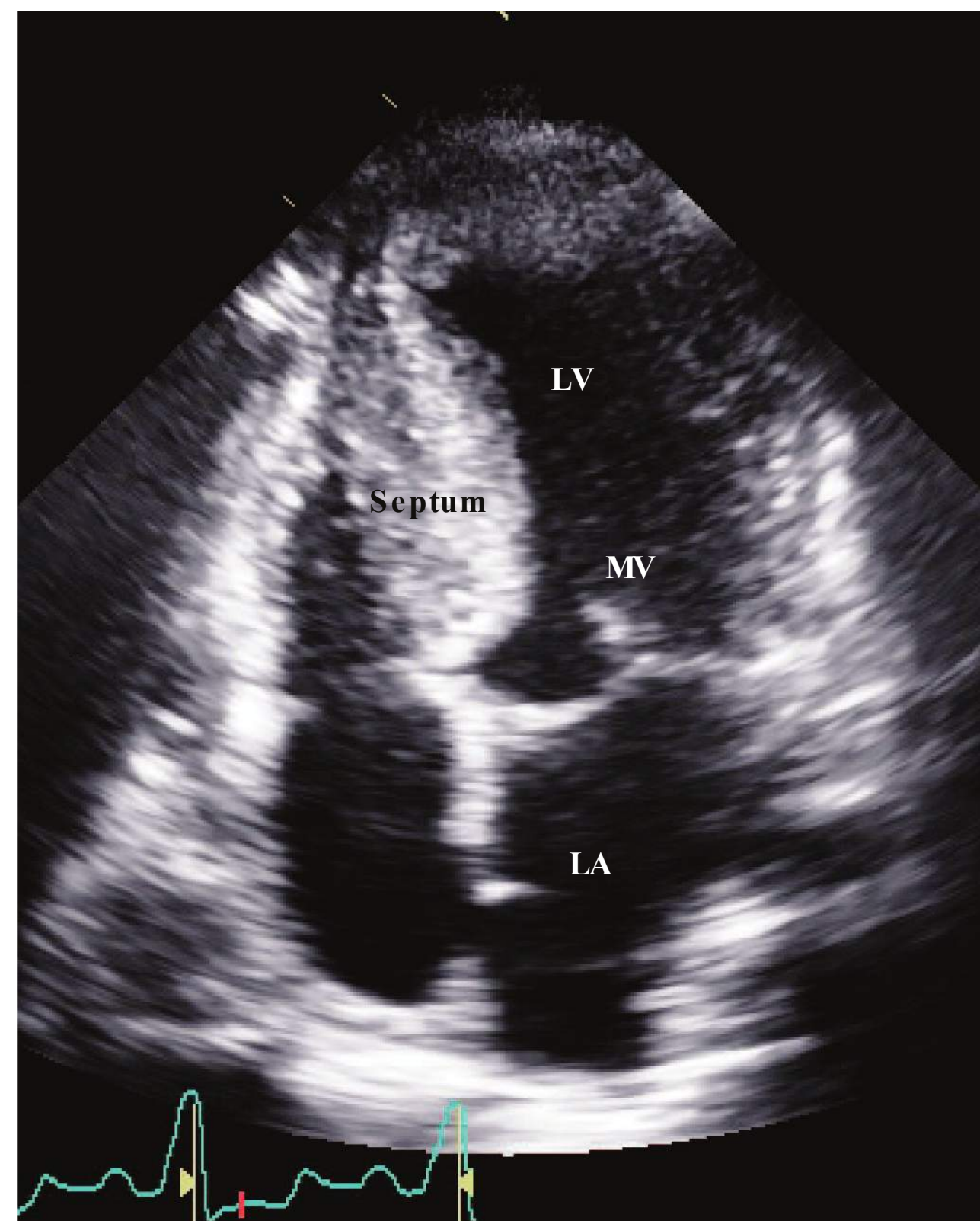


FIGURE 27-16

Hypertrophic cardiomyopathy. This echocardiogram of hypertrophic cardiomyopathy shows asymmetric hypertrophy of the septum compared to the lateral wall of the left ventricle (LV). The mitral valve (MV) is moving anteriorly toward the hypertrophied septum in systole. The left atrium (LA) is enlarged. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

morbidity and mortality, the prognosis for patients diagnosed as adults is generally favorable.

The clustering of hypertrophic cardiomyopathy within families has been appreciated since recognition of the disease approximately 55 years ago. Echocardiographic screening of families revealed an autosomal dominant pattern of inheritance. Initial genetic studies using linkage analysis in large families identified disease-causing mutations in sarcomeric genes. A sarcomere mutation is present in ~60% of patients with hypertrophic cardiomyopathy and is more common in those with familial disease and characteristic asymmetric septal hypertrophy. More than nine different sarcomere genes with over 1400 mutations have been implicated, although ~80% of patients have a mutation in either MYH7 or MYBPC3 (Table 27-3), most of which are unique to individual families ("private" mutations).

Hypertrophic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of left ventricular hypertrophy is rarely present

at birth and usually develops later in life. Accordingly, screening of family members should begin in adolescence and extend through adulthood. In MYBPC3 mutation carriers, the average age of disease development is 40 years, while 30% remain free from hypertrophy after 70 years. Related individuals who carry the same mutation may have a different extent and pattern of hypertrophy (e.g., asymmetric versus concentric), occurrence of outflow tract obstruction, and associated clinical outcomes (e.g., sudden death, atrial fibrillation).

At the level of the sarcomere, hypertrophic cardiomyopathy mutations lead to enhanced calcium sensitivity, maximal force generation, and ATPase activity. Calcium handling is affected through modification of regulatory proteins. Sarcomere mutations lead to abnormal energetics and impaired relaxation, both directly and as a result of hypertrophy. Hypertrophic cardiomyopathy is characterized by misalignment and disarray of the enlarged myofibrils and myocytes (**Fig. 27-17**), which can also occur to a lesser extent in other cardiac diseases. Although hypertrophy is the defining feature of hypertrophic cardiomyopathy, fibrosis and microvascular disease are also present. Interstitial fibrosis is detectable before overt hypertrophy develops and likely results from early activation of profibrotic pathways. In the majority of patients with overt cardiomyopathy, focal areas of replacement fibrosis can be readily detected with MRI. These areas of “scar” may represent substrate for the development of ventricular arrhythmias. Increased thickness and decreased luminal area of the intramural vessels in

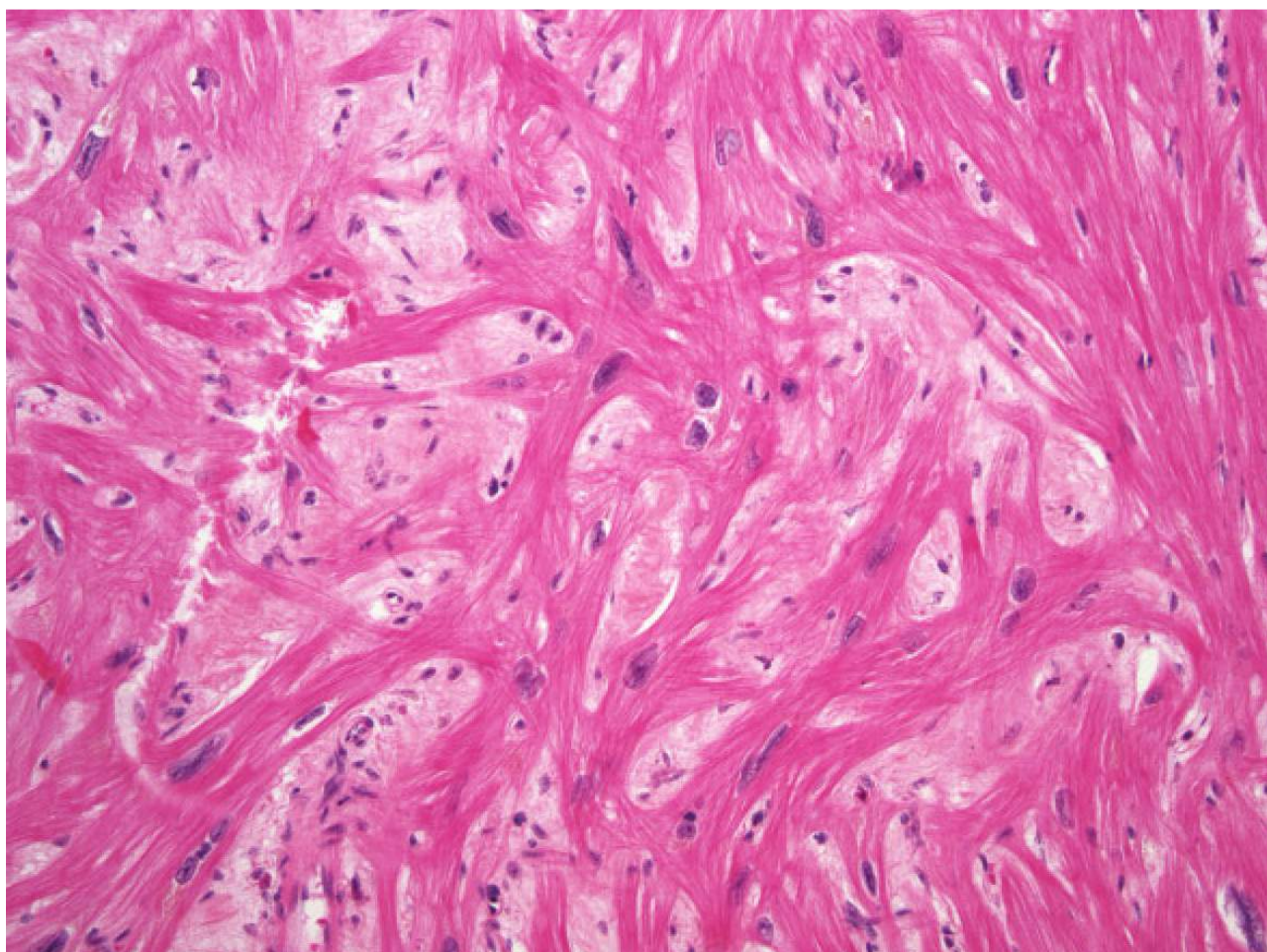


FIGURE 27-17

Hypertrophic cardiomyopathy. Microscopic image of hypertrophic cardiomyopathy showing the characteristic disordered myocyte architecture with swirling and branching rather than the usual parallel arrangement of myocyte fibers. Myocyte nuclei vary markedly in size and interstitial fibrosis is present. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

hypertrophied myocardium contribute to microvascular ischemia and angina. Microinfarction of hypertrophied myocardium is a hypothesized mechanism for replacement scar formation.

Macroscopically, hypertrophy is typically manifest as nonuniform ventricular thickening (**Fig. 27-15**). The interventricular septum is the typical location of maximal hypertrophy, although other patterns of hypertrophic remodeling include concentric and midventricular. Hypertrophy confined to the ventricular apex (apical hypertrophic cardiomyopathy) is less often familial and has a different genetic substrate, with sarcomere mutations present in only ~15%. Left ventricular outflow tract obstruction represents the most common focus of diagnosis and intervention, although diastolic dysfunction, myocardial fibrosis, and microvascular ischemia also contribute to contractile dysfunction and elevated intracardiac pressures. Obstruction is present in ~30% of patients at rest and can be provoked by exercise in another ~30%. Systolic obstruction is initiated by drag forces, which push an anteriorly displaced and enlarged anterior mitral leaflet into contact with the hypertrophied ventricular septum. Mitral leaflet coaptation may ensue, leading to posteriorly directed mitral regurgitation. In order to maintain stroke volume across outflow tract obstruction, the ventricle generates higher pressures, leading to higher wall stress and myocardial oxygen demand. Smaller chamber size and increased contractility exacerbate the severity of obstruction. Conditions of low preload, such as dehydration, and low afterload, such as arterial vasodilation, may lead to transient hypotension and near-syncope. The systolic ejection murmur of left ventricular outflow tract obstruction is harsh and late peaking and can be enhanced by bedside maneuvers that diminish ventricular volume and transiently worsen obstruction, such as standing from a squatting position or the Valsalva maneuver.

DIAGNOSIS

The substantial variability of hypertrophic cardiomyopathy pathology is reflected in the diversity of clinical presentations. Patients may be diagnosed after undergoing evaluations triggered by the abnormal physical findings (murmur) or symptoms of exertional dyspnea, angina, or syncope. Alternatively, diagnosis may follow evaluations prompted by the detection of disease in family members. Cardiac imaging (**Fig. 27-16**) is central to diagnosis due to the insensitivity of examination and ECG and the need to exclude other causes for hypertrophy. The identification of a disease-causing mutation in a proband can focus family evaluations on mutation carriers, but this strategy requires a high degree of certainty that the mutation is truly pathogenic and not a benign DNA variant. Biopsy is not needed to diagnose hypertrophic cardiomyopathy but can be used to exclude

infiltrative and metabolic diseases. Rigorous athletic training (athlete's heart) may cause intermediate degrees of physiologic hypertrophy difficult to differentiate from mild hypertrophic cardiomyopathy. Unlike hypertrophic cardiomyopathy, hypertrophy in the athlete's heart regresses with cessation of training, and is accompanied by supernormal exercise capacity ($\text{VO}_{2\text{max}} > 50 \text{ mL/kg/min}$), mild ventricular dilation, and normal diastolic function.

TREATMENT Hypertrophic Cardiomyopathy

Management focuses on treatment of symptoms and prevention of sudden death and stroke (Fig. 27-18). Left ventricular outflow tract obstruction can be controlled medically in the majority of patients. β -Adrenergic blocking agents and L-type calcium channel blockers (e.g., verapamil) are first-line

agents that reduce the severity of obstruction by slowing heart rate, enhancing diastolic filling, and decreasing contractility. Persistent symptoms of exertional dyspnea or chest pain can sometimes be controlled with the addition of disopyramide, an antiarrhythmic agent with potent negative inotropic properties. Patients with or without obstruction may develop heart failure symptoms due to fluid retention and require diuretic therapies for venous congestion. Severe medically refractory symptoms develop in $\sim 5\%$ of patients, for whom surgical myectomy or alcohol septal ablation may be effective. Developed over 50 years ago, surgical myectomy effectively relieves outflow tract obstruction by excising part of the septal myocardium involved in the dynamic obstruction. In selected patients, perioperative mortality is extremely low with excellent long-term survival free from recurrent obstruction and symptoms. Mitral valve repair or replacement is usually unnecessary as associated eccentric mitral regurgitation resolves with myectomy alone. Alcohol septal ablation in

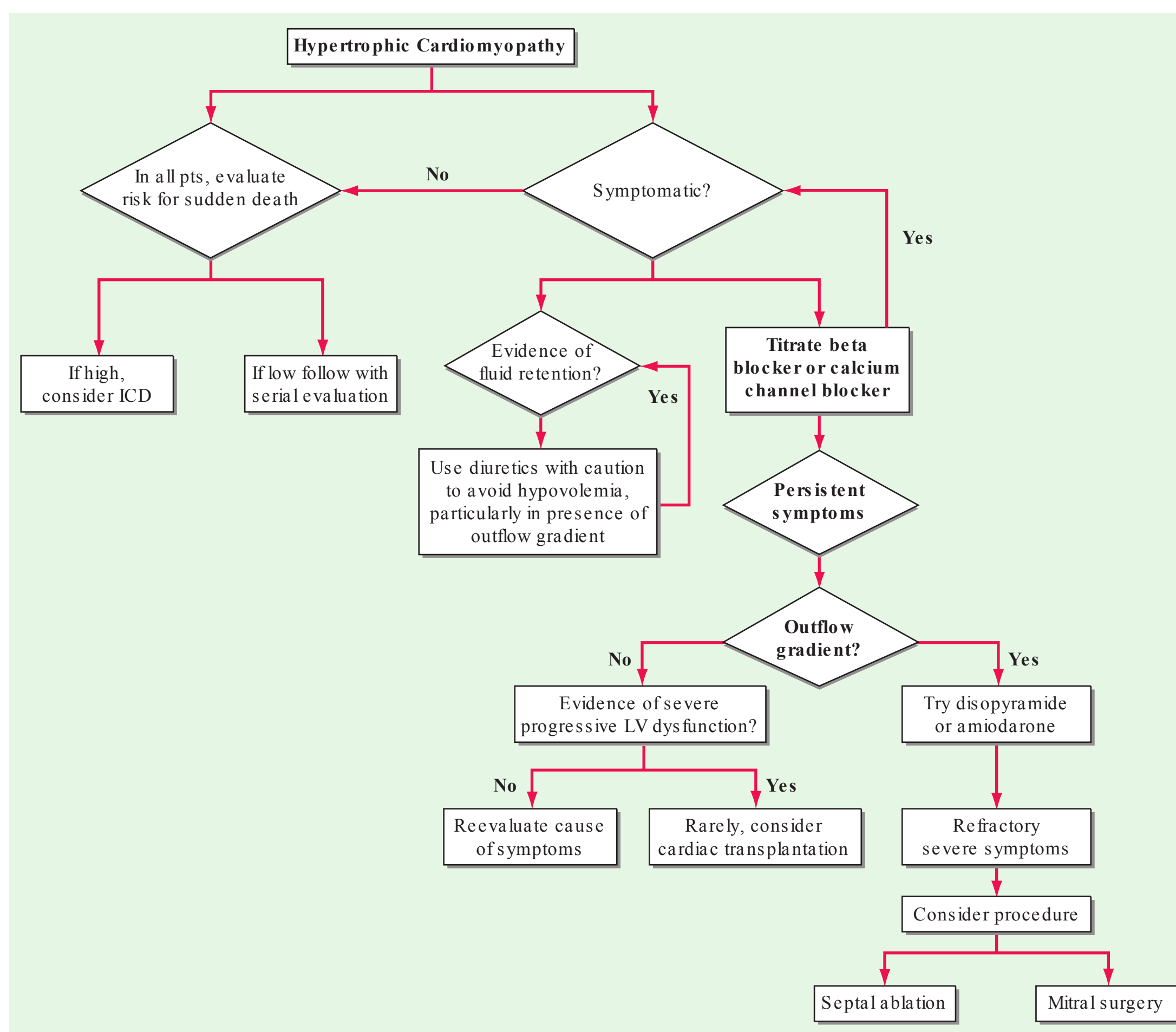


FIGURE 27-18

Treatment algorithm for hypertrophic cardiomyopathy depending on the presence and severity of symptoms and the presence of an intraventricular gradient with obstruction to outflow. Note that all patients with hypertrophic cardiomyopathy should be

evaluated for atrial fibrillation and risk of sudden death, whether or not they require treatment for symptoms. ICD, implantable cardioverter-defibrillator; LV, left ventricular.

322 patients with suitable coronary anatomy can relieve outflow tract obstruction via a controlled infarction of the proximal septum, which produces similar periprocedural outcomes and gradient reduction as surgical myomectomy. Until long-term outcomes are demonstrated for this procedure, it is relegated primarily to patients who wish to avoid surgery or who have limiting comorbidities. Neither procedure has been shown to improve outcomes other than symptoms. With both procedures, the most common complication is the development of complete heart block necessitating permanent pacing. However, ventricular pacing as a primary therapy for outflow tract obstruction is ineffective and not generally advised.

Patients with hypertrophic cardiomyopathy have an increased risk of sudden cardiac death from ventricular tachyarrhythmias. Vigorous physical activity and competitive sport are prohibited. Factors that increase the risk of sudden death from a baseline of 0.5% per year are presented in **Table 27-6**. As sudden death has not been reduced by medical or procedural interventions, an implantable cardioverter-defibrillator is advised for patients with two or more risk factors and is advised on a selected basis for patient with one risk factor. Nevertheless, the positive predictive value of most risk factors is low, and many patients receiving a defibrillator never receive an appropriate therapy. Long-term use of a defibrillator may be associated with serious device-related

complications, particularly in young active patients. Refinement of sudden death risk through the application of contemporary technologies such as cardiac MRI is ongoing.

Atrial fibrillation is common in patients with hypertrophic cardiomyopathy and may lead to hemodynamic deterioration and embolic stroke. Rapid ventricular response is poorly tolerated and may worsen outflow tract obstruction. β -Adrenergic blocking agents and L-type calcium channel blockers slow AV nodal conduction and improve symptoms; cardiac glycosides should be avoided, as they may increase contractility and worsen obstruction. Symptoms exacerbated by atrial fibrillation may persist despite adequate rate control due to loss of AV synchrony and may require restoration of sinus rhythm. Disopyramide and amiodarone are the preferred antiarrhythmic agents, with radiofrequency ablation considered for medically refractory cases. Anticoagulation to prevent embolic stroke in atrial fibrillation is recommended.

Prognosis

The general prognosis for hypertrophic cardiomyopathy is good, better than in early studies of referral populations. For patients diagnosed as adults, survival is comparable to an age-matched population without cardiomyopathy. The sudden death risk is less than 1% per year; however, up to 1 in 20 patients will progress to overt systolic dysfunction with a reduced ejection fraction with or without dilated remodeling (“burned out” or end-stage hypertrophic cardiomyopathy). These patients suffer from low cardiac output and have a high risk of death from progressive heart failure and sudden death unless they undergo cardiac transplantation.

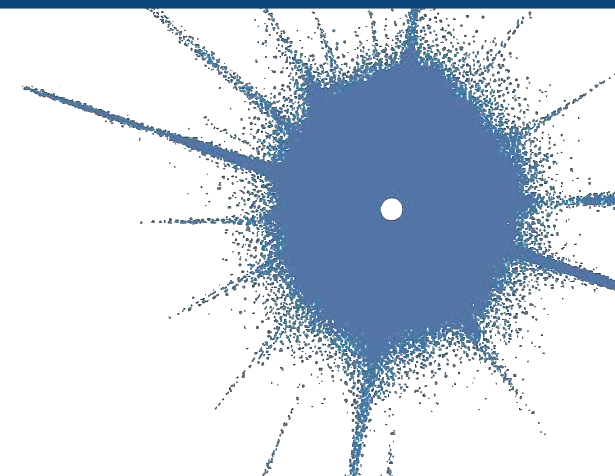
TABLE 27-6
RISK FACTORS FOR SUDDEN DEATH IN HYPERTROPHIC CARDIOMYOPATHY

MAJOR RISK FACTOR		SCREENING TECHNIQUE
History of cardiac arrest or spontaneous sustained ventricular tachycardia ^a		History
Syncope	Nonvagal, often with or after exertion	History
Family history of sudden cardiac death		Family history
Spontaneous non-sustained ventricular tachycardia ^b	>3 beats at rate >120	Exercise or 24- to 48-hour ambulatory recording
LV thickness >30 mm	Present in <10% of patients	Echocardiography
Abnormal blood pressure response to exercise ^b	Systolic blood pressure fall or failure to increase at peak exercise	Maximal upright exercise testing

^aImplantable cardioverter-defibrillator advised for patients with prior arrest or sustained ventricular tachycardia regardless of other risk factors.
^b Prognostic value most applicable to patients less than 40 years old.
Abbreviation: LV, left ventricle.

CHAPTER 28

PERICARDIAL DISEASE



Eugene Braunwald

NORMAL FUNCTIONS OF THE PERICARDIUM

The normal pericardium is a double-layered sac; the visceral pericardium is a serous membrane that is separated by a small quantity (15–50 mL) of fluid, an ultrafiltrate of plasma, from the fibrous parietal pericardium. The normal pericardium, by exerting a restraining force, prevents sudden dilation of the cardiac chambers, especially the right atrium and ventricle, during exercise and with hypervolemia. It also restricts the anatomic position of the heart, and probably retards the spread of infections from the lungs and pleural cavities to the heart. Nevertheless, total absence of the pericardium, either congenital or after surgery, does not produce obvious clinical disease. In partial left pericardial defects, the main pulmonary artery and left atrium may bulge through the defect; very rarely, herniation and subsequent strangulation of the left atrium may cause sudden death.

ACUTE PERICARDITIS

Acute pericarditis, by far the most common pathologic process involving the pericardium (**Table 28-1**), has four principal diagnostic features:

1. Chest pain is usually present in acute infectious pericarditis and in many of the forms presumed to be related to hypersensitivity or autoimmunity. The pain of acute pericarditis is often severe, retrosternal, and left precordial, and referred to the neck, arms, or left shoulder. Frequently the pain is pleuritic, consequent to accompanying pleural inflammation (i.e., sharp and aggravated by inspiration and coughing), but sometimes it is steady, constricting, radiates into either arm or both arms, and
2. A pericardial friction rub is audible at some point in about 85% of patients with acute pericarditis, may have up to three components per cardiac cycle, is high-pitched, and is described as rasping, scratching, or grating (**Chap. 9**). It is heard most frequently at end expiration with the patient upright and leaning forward.
3. The electrocardiogram (ECG) in acute pericarditis without massive effusion usually displays changes secondary to acute subepicardial inflammation (**Fig. 28-1**). It typically evolves through four stages. In stage 1, there is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V_2 to V_6 , with reciprocal depressions only in aVR and sometimes V_1 . Also, there is depression of the PR segment below the TP segment, reflecting atrial involvement.

resembles that of myocardial ischemia; therefore, confusion with acute myocardial infarction (AMI) is common. Characteristically, however, pericardial pain may be relieved by sitting up and leaning forward and is intensified by lying supine (**Chap. 4**). Pain is often absent in slowly developing tuberculous, postirradiation, and neoplastic, uremic, and constrictive pericarditis.

The differentiation of AMI from acute pericarditis may become perplexing when, with acute pericarditis, serum biomarkers of myocardial damage such as troponin and creatine kinase-MB rise, presumably because of concomitant involvement of the epicardium in the inflammatory process (an epimyocarditis) with resulting myocyte necrosis. However, these elevations, if they occur, are quite modest given the extensive electrocardiographic ST-segment elevation in pericarditis. Tis dissociation is useful in differentiating between these conditions.

TABLE 28-1

CLASSIFICATION OF PERICARDITIS	
CLINICAL CLASSIFICATION	
I. Acute pericarditis (<6 weeks)	
A. Fibrinous	
B. Effusive (serous or sanguineous)	
II. Subacute pericarditis (6 weeks to 6 months)	
A. Effusive-constrictive	
B. Constrictive	
III. Chronic pericarditis (>6 months)	
A. Constrictive	
B. Effusive	
C. Adhesive (nonconstrictive)	
Etiologic Classification	
I. Infectious pericarditis	
A. Viral (coxsackievirus A and B, echovirus, mumps, adenovirus, hepatitis, HIV)	
B. Pyogenic (pneumococcus, Streptococcus, Staphylococcus, Neisseria, Legionella)	
C. Tuberculous	
D. Fungal (histoplasmosis, coccidioidomycosis, Candida, blastomycosis)	
E. Other infections (syphilitic, protozoal, parasitic)	
II. Noninfectious pericarditis	
A. Acute myocardial infarction	
B. Uremia	
C. Neoplasia	
1. Primary tumors (benign or malignant, mesothelioma)	
2. Tumors metastatic to pericardium (lung and breast cancer, lymphoma, leukemia)	
D. Myxedema	
E. Cholesterol	
F. Chylopericardium	
G. Trauma	
1. Penetrating chest wall	
2. Nonpenetrating	
H. Aortic dissection (with leakage into pericardial sac)	
I. Postirradiation	
J. Familial Mediterranean fever	
K. Familial pericarditis	
1. Mulibrey nanism ^a	
L. Acute idiopathic	
M. Whipple's disease	
N. Sarcoidosis	
III. Pericarditis presumably related to hypersensitivity or autoimmunity	
A. Rheumatic fever	
B. Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, acute rheumatic fever, granulomatosis with polyangiitis [Wegener's])	
C. Drug-induced (e.g., procainamide, hydralazine, phenytoin, isoniazid, minoxidil, anticoagulants, methysergide)	
D. Postcardiac injury	
1. Postmyocardial infarction (Dressler's syndrome)	
2. Postpericardiotomy	
3. Posttraumatic	

^aAn autosomal recessive syndrome characterized by growth failure, muscle hypotonia, hepatomegaly, ocular changes, enlarged cerebral ventricles, mental retardation, ventricular hypertrophy, and chronic constrictive pericarditis

Usually there are no significant changes in QRS complexes. After several days, the ST segments return to normal (stage 2), and only then, or even later, do the T waves become inverted (stage 3). Weeks or months after the onset of acute pericarditis, the ECG returns to normal (stage 4). In contrast, in AMI, ST elevations are convex, and reciprocal depression is usually more prominent; these changes may return to normal within a day or two. Q waves may develop, with loss of R-wave amplitude, and T-wave inversions are usually seen within hours before the ST segments have become isoelectric (**Chaps. 40 and 41**).

4. Pericardial effusion is usually associated with pain and/or the ECG changes mentioned above, as well as electrical alternans. Pericardial effusion is especially important clinically when it develops within a relatively short time because it may lead to cardiac tamponade (see below). Differentiation from cardiac enlargement may be difficult on physical examination, but heart sounds may be fainter with pericardial effusion. The friction rub and the apex impulse may disappear. The base of the left lung may be compressed by pericardial fluid, producing Ewart's sign, a patch of dullness and increased fremitus (and egophony) beneath the angle of the left scapula. The chest roentgenogram may show enlargement of the cardiac silhouette, with a "water bottle" configuration, but may be normal.

Diagnosis

Echocardiography (**Chap. 12**) is the most widely used imaging technique. It is sensitive, specific, simple, noninvasive, may be performed at the bedside, and can identify accompanying cardiac tamponade (see below) (**Fig. 28-2**). The presence of pericardial fluid is recorded by two-dimensional transthoracic echocardiography as a relatively echo-free space between the posterior pericardium and left ventricular epicardium in patients with small effusions and as a space between the anterior right ventricle and the parietal pericardium just beneath the anterior chest wall. In patients with large effusions, the heart may swing freely within the pericardial sac. When severe, the extent of this motion alternates and may be associated with electrical alternans (**Fig. 28-3**). Echocardiography allows localization and identification of the quantity of pericardial fluid.

The diagnosis of pericardial fluid or thickening may be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). These techniques may be superior to echocardiography in detecting loculated pericardial effusions, pericardial thickening, and the identification of pericardial masses.

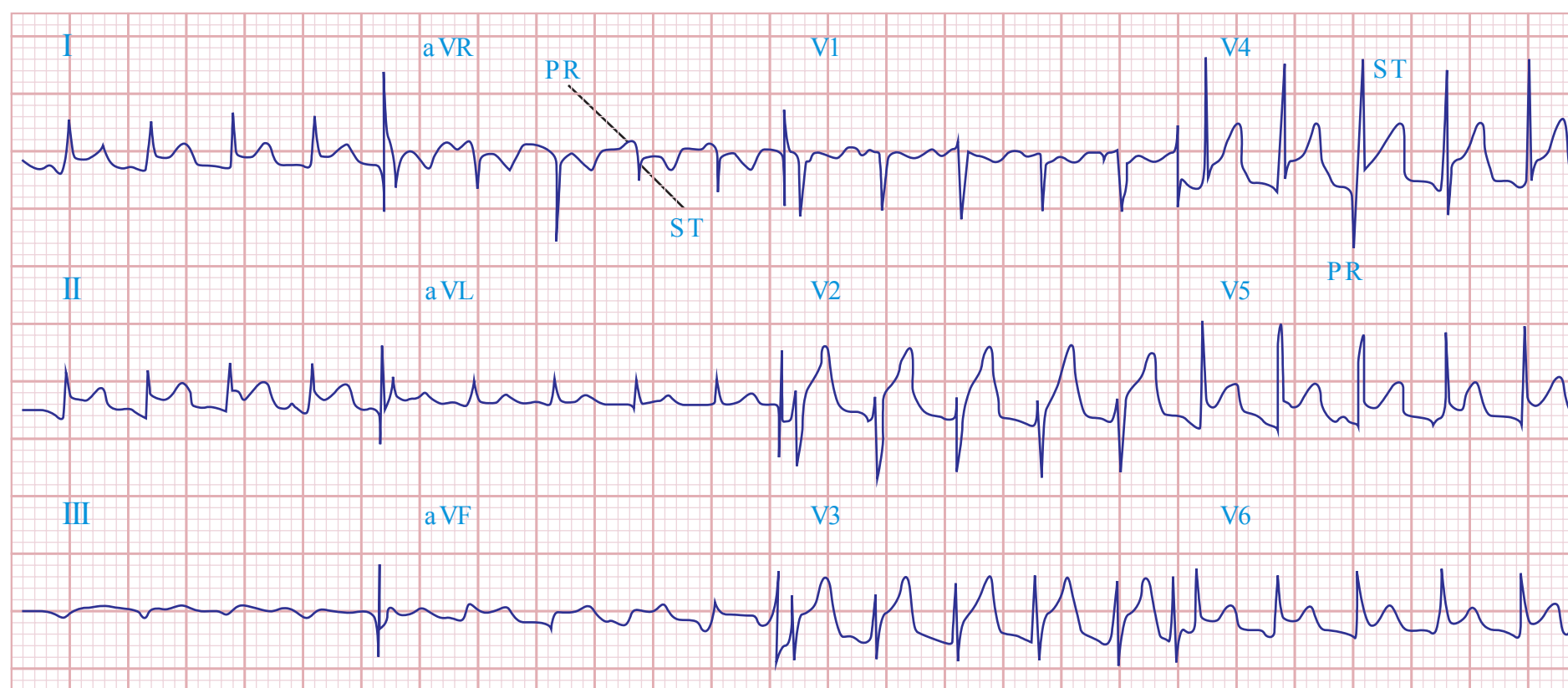


FIGURE 28-1

Acute pericarditis. There are diffuse ST-segment elevations (in this case in leads I, II, aVF, and V₂ to V₆) due to a ventricular current

of injury. There is PR-segment deviation (opposite in polarity to the ST segment) due to a concomitant atrial injury current.

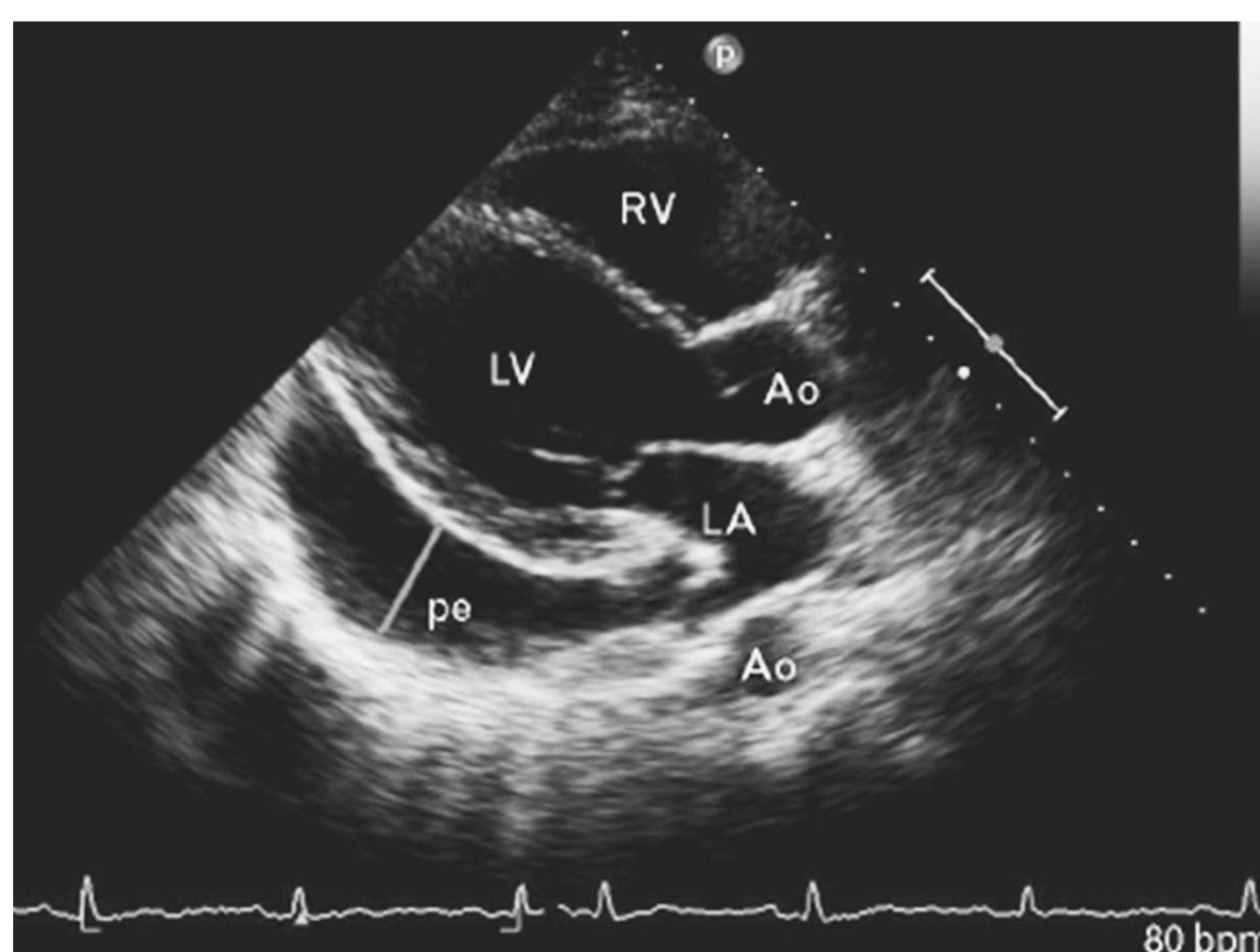


FIGURE 28-2

Two-dimensional echocardiogram in lateral view in a patient with a large pericardial effusion. Ao, aorta; LV, left ventricle; pe,

pericardial effusion; RV, right ventricle. (From M Imazio: Curr Opin Cardiol 27:308, 2012.)

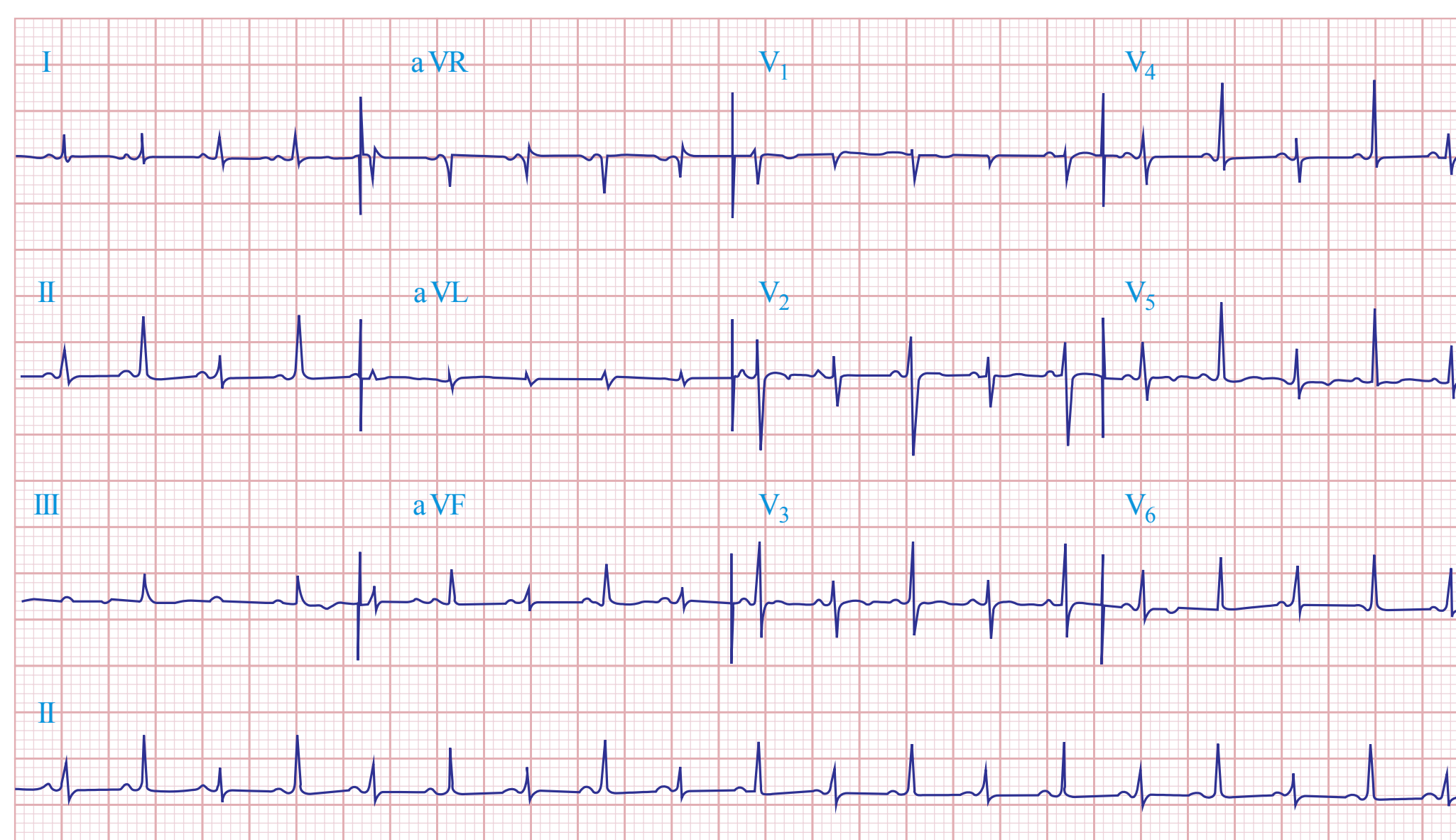


FIGURE 28-3

Electrical alternans. This tracing was obtained from a patient with a large pericardial effusion with tamponade. (Reproduced from DM Mirvis, AL Goldberger: Electrocardiography, in RO Bonow et al [eds]: Braunwald's Heart Disease, 9th ed. Philadelphia: Elsevier, 2012.)

TREATMENT Acute Pericarditis

There is no specific therapy for acute idiopathic pericarditis, but bed rest and anti-inflammatory treatment with aspirin (2–4 g/d), with gastric protection (e.g., omeprazole 20 mg/d), may be given. If this is ineffective, one of the non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (400–600 mg tid) or indomethacin (25–50 mg tid), should be tried. In responsive patients, these doses should be continued for 1–2 weeks and then tapered over several weeks. In patients who are unresponsive, colchicine (0.5 mg bid, given for 4–8 weeks) has been found to be effective, not only in acute pericarditis, but also in reducing the risk of recurrent pericarditis. Colchicine is concentrated in and interferes with the migration of neutrophils, is contraindicated in patients with hepatic or renal dysfunction, and may cause diarrhea and other gastrointestinal side effects. Glucocorticoids (e.g., prednisone 1 mg/kg per day) usually suppress the clinical manifestations of acute pericarditis in patients who have failed therapy with the anti-inflammatory therapies described above, but appear to increase the risk of subsequent recurrence. Therefore, full-dose corticosteroids should be given for only 2–4 days and then tapered. Anticoagulants should be avoided because their use could cause bleeding into the pericardial cavity and tamponade.

In patients with recurrences that are multiple, frequent, disabling, continue for more than 2 years, and are not prevented by colchicine and other NSAIDs and are not controlled by glucocorticoids, pericardial stripping may be necessary to terminate the illness, and usually does so.

CARDIAC TAMPONADE

The accumulation of fluid in the pericardial space in a quantity sufficient to cause serious obstruction of the inflow of blood into the ventricles results in cardiac tamponade. This complication may be fatal if it is not recognized and treated promptly. The most common causes of tamponade are idiopathic pericarditis and pericarditis secondary to neoplastic disease. Tamponade may also result from bleeding into the pericardial space after leakage from an aortic dissection, cardiac operations, trauma, and treatment of patients with acute pericarditis with anticoagulants.

The three principal features of tamponade (Beck's triad) are hypotension, soft or absent heart sounds, and jugular venous distention with a prominent x descent but an absent y descent. The limitations of ventricular filling are responsible for a reduction of cardiac output. The quantity of fluid necessary to produce cardiac tamponade may be as small as 200 mL when the fluid develops rapidly to as much as >2000 mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing

volume. Tamponade may also develop more slowly, and in these circumstances, the clinical manifestations can resemble those of heart failure, including dyspnea, orthopnea, and hepatic engorgement.

A high index of suspicion for cardiac tamponade is required because in many instances no obvious cause for pericardial disease is apparent, and this diagnosis should be considered in any patient with otherwise unexplained enlargement of the cardiac silhouette, hypotension, and elevation of jugular venous pressure. There may be reduction in amplitude of the QRS complexes, and electrical alternans of the P, QRS, or T waves should raise the suspicion of cardiac tamponade (Fig. 28-3).

Table 28-2 lists the features that distinguish acute cardiac tamponade from constrictive pericarditis.

Paradoxical pulse

This important clue to the presence of cardiac tamponade consists of a greater than normal (10 mmHg) inspiratory decline in systolic arterial pressure. When severe, it may be detected by palpating weakness or disappearance of the arterial pulse during inspiration, but usually sphygmomanometric measurement of systolic pressure during slow respiration is required.

Because both ventricles share a tight incompressible covering, i.e., the pericardial sac, the inspiratory enlargement of the right ventricle in cardiac tamponade compresses and reduces left ventricular volume; leftward bulging of the interventricular septum reduces further the left ventricular cavity as the right ventricle enlarges during inspiration. Thus, in cardiac tamponade, the normal inspiratory augmentation of right ventricular volume causes an exaggerated reduction of left ventricular volume, stroke volume, and systolic pressure. Paradoxical pulse also occurs in approximately one-third of patients with constrictive pericarditis (see below), and in some cases of hypovolemic shock, acute and chronic obstructive airway disease, and pulmonary embolus. Right ventricular infarction (**Chap. 41**) may resemble cardiac tamponade with hypotension, elevated jugular venous pressure, an absent y descent in the jugular venous pulse, and, occasionally, a paradoxical pulse (Table 28-2).

Low-pressure tamponade refers to mild tamponade in which the intrapericardial pressure is increased from its slightly subatmospheric levels to +5 to +10 mmHg; in some instances, hypovolemia coexists. As a consequence, the central venous pressure is normal or only slightly elevated, whereas arterial pressure is unaffected and there is no paradoxical pulse. These patients are asymptomatic or complain of mild weakness and dyspnea. The diagnosis is aided by echocardiography, and both hemodynamic and clinical manifestations improve after pericardiocentesis.

TABLE 28-2
FEATURES THAT DISTINGUISH CARDIAC TAMPONADE FROM CONSTRICTIVE PERICARDITIS AND SIMILAR CLINICAL DISORDERS

CHARACTERISTIC	TAMPONADE	CONSTRICTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY	RVMI	EFFUSIVE CONSTRICTIVE PERICARDITIS
Clinical					
Pulsus paradoxus	+++	+	+	+	+++
Jugular veins					
Prominent y descent	—	++	+	+	—
Prominent x descent	+++	++	+++	+	+++
Kussmaul’s sign	—	+++	+	+++	++
Third heart sound	—	—	+	+	+
Pericardial knock	—	++	—	—	—
Electrocardiogram					
Low ECG voltage	++	++	++	—	++
Electrical alternans	++	—	—	—	+
Echocardiogram					
Thickened pericardium	—	+++	—	—	++
Pericardial calcification	—	++	—	—	
Pericardial effusion	+++	—	—	++	
RV size	Usually small	Usually normal	Usually normal	Enlarged	
RA and RV	+++	—	—	—	
Exaggerated respiratory variation in flow velocity	+++	+++	—	+++	
CT/MRI					
Thickened pericardium	—	+++	—	++	
Cardiac catheterization					
Equalization of diastolic pressures	+++	+++	—	++	

Abbreviations: +++, always present; ++, usually present; +, rare;—, absent; DC, diastolic collapse; ECG, electrocardiograph; RA, right atrium; RV, right ventricle; RVMI, right ventricular myocardial infarction.
Source: Adapted from GM Brockington et al: Cardiol Clin 8:645, 1990, with permission.

Diagnosis

Because immediate treatment of cardiac tamponade may be lifesaving, prompt measures to establish the diagnosis by echocardiography should be undertaken. When pericardial effusion causes tamponade, Doppler ultrasound shows that tricuspid and pulmonic valve flow velocities increase markedly during inspiration, whereas pulmonic vein, mitral, and aortic flow velocities diminish (as in constrictive pericarditis, see below) (Fig. 28-4). In tamponade, there is late diastolic inward motion (collapse) of the right ventricular free wall and the right atrium. Transesophageal echocardiography, CT, or cardiac MRI may be necessary to diagnose a loculated effusion responsible for cardiac tamponade.

TREATMENT Cardiac Tamponade

Patients with acute pericarditis should be observed frequently for the development of an effusion; if a large effusion is present, pericardiocentesis should be carried out or the patient watched closely for signs of tamponade. Arterial and venous pressures should be monitored and serial echocardiograms obtained.

PERICARDIOCENTESIS If manifestations of tamponade appear, echocardiographically guided pericardiocentesis using an apical, parasternal, or, most commonly, subxiphoid approach must be carried out at once because reduction of the elevated intrapericardial pressure may be lifesaving. Intravenous saline may be administered as the patient is being readied for the procedure, but the pericardiocentesis must not be delayed.

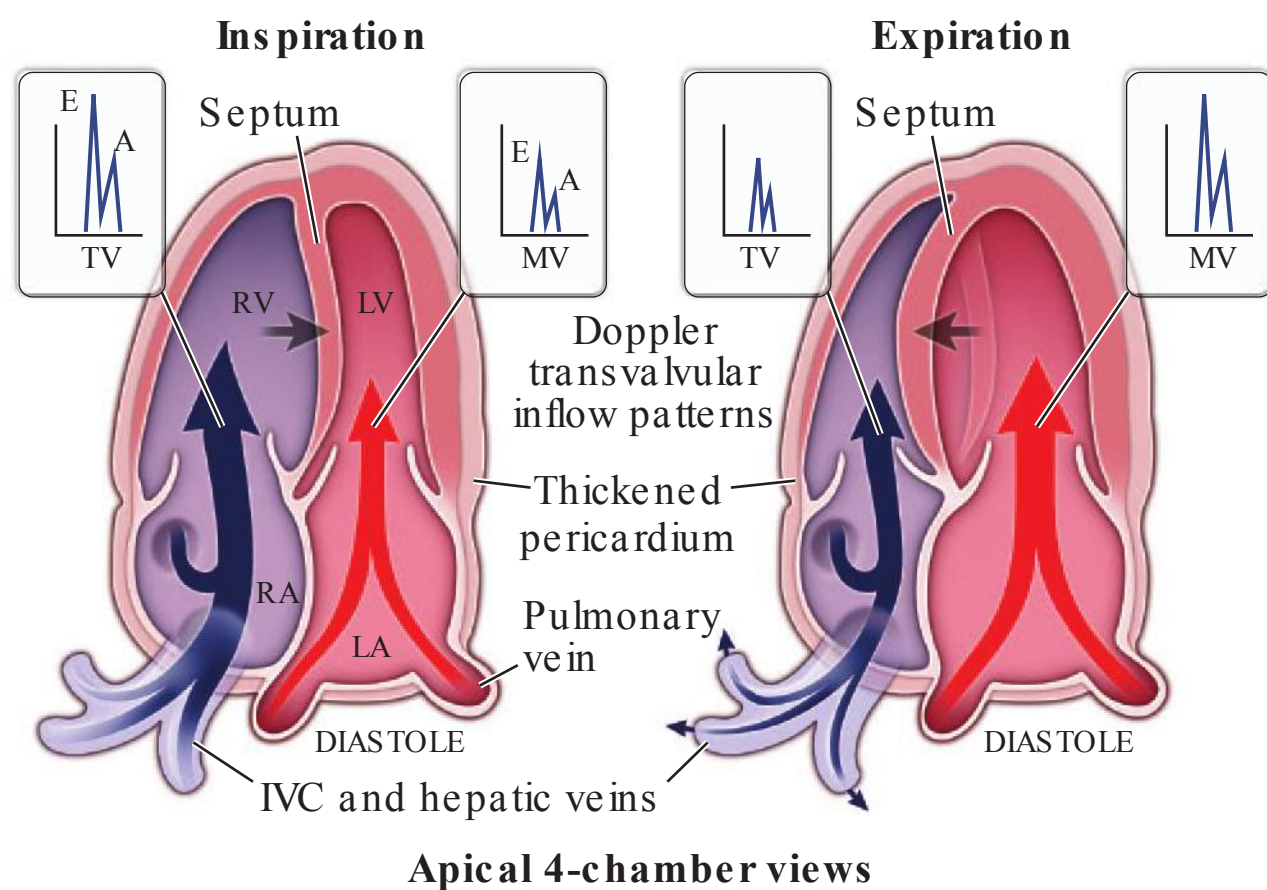


FIGURE 28-4

Constrictive pericarditis. Doppler schema of respirophasic changes in mitral and tricuspid inflow. Reciprocal patterns of ventricular filling are assessed on pulsed Doppler examination of mitral valve (MV) and tricuspid valve (TV) inflow. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Courtesy of Bernard E. Bulwer, MD; with permission.)

If possible, intrapericardial pressure should be measured before fluid is withdrawn, and the pericardial cavity should be drained as completely as possible. A small, multiholed catheter advanced over the needle inserted into the pericardial cavity may be left in place to allow draining of the pericardial space if fluid reaccumulates. Surgical drainage through a limited (sub-xiphoid) thoracotomy may be required in recurrent tamponade, when it is necessary to remove loculated effusions, and/or when it is necessary to obtain tissue for diagnosis.

Pericardial fluid obtained from an effusion often has the physical characteristics of an exudate. Bloody fluid is most commonly due to neoplasm, renal failure, or dialysis in the United States and tuberculosis in developing nations but may also be found in the effusion of acute rheumatic fever, after cardiac injury, and after myocardial infarction. Transudative pericardial effusions may occur in heart failure.

The pericardial fluid should be analyzed for red and white blood cells and cytologic studies, and cultures should be obtained. The presence of DNA of *Mycobacterium tuberculosis* determined by the polymerase chain reaction strongly supports the diagnosis of tuberculous pericarditis.

VIRAL OR IDIOPATHIC ACUTE PERICARDITIS

In many instances, acute pericarditis occurs in association with illnesses of known or presumed viral origin and probably is caused by the same agent. Commonly, there is an antecedent infection of the respiratory tract, and viral isolation and serologic studies are negative. In some cases, coxsackievirus A or B or the virus of influenza, echovirus, mumps, herpes simplex, chickenpox, adenovirus,

or cytomegalovirus has been isolated from pericardial fluid and/or appropriate elevations in viral antibody titers have been noted. Pericardial effusion is a common cardiac manifestation of HIV; it is usually secondary to infection (often mycobacterial) or neoplasm, most often lymphoma. Frequently, a viral cause cannot be established, and the term idiopathic acute pericarditis is then appropriate.

Viral or idiopathic acute pericarditis occurs at all ages but is more common in young adults and is often associated with pleural effusions and pneumonitis. The almost simultaneous development of fever and precordial pain, often 10–12 days after a presumed viral illness, constitutes an important feature in the differentiation of acute pericarditis from AMI, in which chest pain precedes fever. The constitutional symptoms are usually mild to moderate, and a pericardial friction rub is often audible. The disease ordinarily runs its course in a few days to 4 weeks. The ST-segment alterations in the ECG usually disappear after 1 or more weeks, but the abnormal T waves may persist for several years and be a source of confusion in persons without a clear history of pericarditis. Pleuritis and pneumonitis frequently accompany viral or idiopathic acute pericarditis. Accumulation of some pericardial fluid is common, and both tamponade and constrictive pericarditis are possible, but infrequent, complications.

The most frequent complication is recurrent (relapsing) pericarditis, which occurs in about one-fourth of patients with acute idiopathic pericarditis. In a smaller number, there are multiple recurrences. For treatment, see earlier section on treatment of acute pericarditis.

Postcardiac injury syndrome

Acute pericarditis may appear in a variety of circumstances that have one common feature—previous injury to the myocardium with blood in the pericardial cavity. The syndrome may develop after a cardiac operation (postpericardiotomy syndrome), after blunt or penetrating cardiac trauma (**Chap. 29**), or after perforation of the heart with a catheter. Rarely, it follows AMI.

The clinical picture mimics acute viral or idiopathic pericarditis. The principal symptom is the pain of acute pericarditis, which usually develops 1–4 weeks after the cardiac injury but earlier (1–3 days) after AMI. Recurrences are common and may occur up to 2 years or more following the injury. Fever, pleuritis, and pneumonitis are the outstanding features, and the bout of illness usually subsides in 1 or 2 weeks. The pericarditis may be of the fibrinous variety, or it may be a pericardial effusion, which is often serosanguineous but rarely causes tamponade. ECG changes typical of acute pericarditis may also occur. This syndrome is probably the result of a hypersensitivity reaction to antigen(s) that originate from injured myocardial tissue and/or pericardium.

Often no treatment is necessary aside from aspirin and analgesics. When the illness is severe or followed by a series of disabling recurrences, therapy with an NSAID, colchicine, or a glucocorticoid, such as described for treatment of acute pericarditis, is usually effective.

DIFFERENTIAL DIAGNOSIS

Because there is no specific test for acute idiopathic pericarditis, the diagnosis is one of exclusion. Consequently, all other disorders that may be associated with acute fibrinous pericarditis must be considered. A common diagnostic error is mistaking acute viral or idiopathic pericarditis for AMI and vice versa. When acute fibrinous pericarditis is associated with AMI (**Chap. 41**), it is characterized by fever, pain, and a friction rub in the first 4 days after the development of the infarct. ECG abnormalities (such as the appearance of Q waves, brief ST-segment elevations with reciprocal changes, and earlier T-wave changes in AMI) and the extent of the elevations of markers of myocardial necrosis (higher in AMI) are helpful in differentiating pericarditis from AMI.

Pericarditis secondary to postcardiac injury is differentiated from acute idiopathic pericarditis chiefly by timing. If it occurs within a few days or weeks of an AMI, a chest blow, a cardiac perforation, or a cardiac operation, it may be justified to conclude that the two are probably related.

It is important to distinguish pericarditis due to collagen vascular disease from acute idiopathic pericarditis. Most important in the differential diagnosis is the pericarditis due to systemic lupus erythematosus (SLE) or drug-induced (procainamide or hydralazine) lupus. When pericarditis occurs in the absence of any obvious underlying disorder, the diagnosis of SLE may be suggested by a rise in the titer of antinuclear antibodies. Acute pericarditis is an occasional complication of rheumatoid arthritis, scleroderma, and polyarteritis nodosa, and other evidence of these diseases is usually obvious.

Pyogenic (purulent) pericarditis is usually secondary to cardiothoracic operations, by extension of infection from the lungs or pleural cavities, from rupture of the esophagus into the pericardial sac, or from rupture of a ring abscess in a patient with infective endocarditis. It may also complicate the viral, pyogenic, mycobacterial, and fungal infections that occur with HIV infection. It is generally accompanied by fever, chills, septicemia, and evidence of infection elsewhere and generally has a poor prognosis. The diagnosis is made by examination of the pericardial fluid. It requires drainage as well as vigorous antibiotic treatment.

Pericarditis of renal failure occurs in up to one-third of patients with chronic uremia (uremic pericarditis),

and is also seen in patients undergoing chronic dialysis who have normal levels of blood urea and creatinine (dialysis-associated pericarditis). These two forms of pericarditis may be fibrinous and are generally associated with serosanguineous effusions. A pericardial friction rub is common, but pain is usually absent or mild. Treatment with an NSAID and intensification of dialysis are usually adequate. Occasionally, tamponade occurs and pericardiocentesis is required. When the pericarditis of renal failure is recurrent or persistent, a pericardial window should be created or pericardiectomy may be necessary.

Pericarditis due to neoplastic diseases results from extension or invasion of metastatic tumors (most commonly carcinoma of the lung and breast, malignant melanoma, lymphoma, and leukemia) to the pericardium; pain, atrial arrhythmias, and tamponade are complications that occur occasionally. Diagnosis is made by pericardial fluid cytology or pericardial biopsy. Mediastinal irradiation for neoplasm may cause acute pericarditis and/or chronic constrictive pericarditis. Unusual causes of acute pericarditis include syphilis, fungal infection (histoplasmosis, blastomycosis, aspergillosis, and candidiasis), and parasitic infestation (amebiasis, toxoplasmosis, echinococcosis, and trichinosis).

CHRONIC PERICARDIAL EFFUSIONS

Chronic pericardial effusions are sometimes encountered in patients without an antecedent history of acute pericarditis. They may cause few symptoms per se, and their presence may be detected by finding an enlarged cardiac silhouette on a chest roentgenogram. Tuberculosis is a common cause. Myxedema may be responsible for chronic pericardial effusion that is sometimes massive but rarely, if ever, causes cardiac tamponade. The cardiac silhouette may be markedly enlarged, and an echocardiogram distinguishes cardiomegaly from pericardial effusion. The diagnosis of myxedema can be confirmed by tests of thyroid function. Myxedematous pericardial effusion responds to thyroid hormone replacement. Neoplasms, SLE, rheumatoid arthritis, mycotic infections, radiation therapy to the chest, pyogenic infections, and chylopericardium may also cause chronic pericardial effusion and should be considered and specifically sought in such patients.

Aspiration and analysis of the pericardial fluid are often helpful in diagnosis. Pericardial fluid should be analyzed as described in pericardiocentesis. Grossly sanguineous pericardial fluid results most commonly from a neoplasm, tuberculosis, renal failure, or slow leakage from an aortic dissection. Pericardiocentesis may resolve large effusions, but pericardiectomy may be required in patients with recurrence. Intrapericardial instillation of sclerosing agents may be used to prevent reaccumulation of fluid.

This disorder results when the healing of an acute fibrinous or serofibrinous pericarditis or the resorption of a chronic pericardial effusion is followed by obliteration of the pericardial cavity with the formation of granulation tissue. The latter gradually contracts and forms a firm scar encasing the heart, which may be calcified. In developing nations where the condition is prevalent, a high percentage of cases are of tuberculous origin, but this is now an uncommon cause in North America. Chronic constrictive pericarditis may follow acute or relapsing viral or idiopathic pericarditis, trauma with organized blood clot, or cardiac surgery of any type or result from mediastinal irradiation, purulent infection, histoplasmosis, neoplastic disease (especially breast cancer, lung cancer, and lymphoma), rheumatoid arthritis, SLE, or chronic renal failure treated by chronic dialysis. In many patients, the cause of the pericardial disease is undetermined, and in these patients, an asymptomatic or forgotten bout of viral pericarditis, acute or idiopathic, may have been the inciting event.

The basic physiologic abnormality in patients with chronic constrictive pericarditis is the inability of the ventricles to fill because of the limitations imposed by the rigid, thickened pericardium. Ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, whereas in cardiac tamponade, ventricular filling is impeded throughout diastole. In both conditions, ventricular end-diastolic and stroke volumes are reduced and the end-diastolic pressures in both ventricles and the mean pressures in the atria, pulmonary veins, and systemic veins are all elevated to similar levels (i.e., within 5 mmHg of one another). Despite these hemodynamic changes, systolic function may be normal or only slightly impaired. However, in advanced cases, the fibrotic process may extend into the myocardium and cause myocardial scarring and atrophy, and venous congestion may then be due to the combined effects of the pericardial and myocardial lesions.

In constrictive pericarditis, the right and left atrial pressure pulses display an M-shaped contour, with prominent x and y descents. The y descent, which is absent or diminished in cardiac tamponade, is the most prominent deflection in constrictive pericarditis; it reflects rapid early filling of the ventricles. The y descent is interrupted by a rapid rise in atrial pressure during early diastole, when ventricular filling is impeded by the constricting pericardium. These characteristic changes are transmitted to the jugular veins, where they may be recognized by inspection. In constrictive pericarditis, the ventricular pressure pulses in both ventricles exhibit characteristic “square root” signs during diastole. These

hemodynamic changes, although characteristic, are not pathognomonic of constrictive pericarditis and may also be observed in restrictive cardiomyopathies (**Chap. 27, Table 27-2**).

CLINICAL AND LABORATORY FINDINGS

Weakness, fatigue, weight gain, increased abdominal girth, abdominal discomfort, and edema are common. The patient often appears chronically ill, and in advanced cases, anasarca, skeletal muscle wasting, and cachexia may be present. Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe. Acute left ventricular failure (acute pulmonary edema) is very uncommon. The cervical veins are distended and may remain so even after intensive diuretic treatment, and venous pressure may fail to decline during inspiration (Kussmaul's sign). The latter is common in chronic pericarditis but may also occur in tricuspid stenosis, right ventricular infarction, and restrictive cardiomyopathy.

The pulse pressure is normal or reduced. A paradoxical pulse can be detected in about one-third of cases. Congestive hepatomegaly is pronounced and may impair hepatic function and cause jaundice; ascites is common and is usually more prominent than dependent edema. The apical pulse is reduced and may retract in systole (Broadbent's sign). The heart sounds may be distant; an early third heart sound (i.e., a pericardial knock, occurring at the cardiac apex 0.09–0.12 s after aortic valve closure) with the abrupt cessation of ventricular filling is often conspicuous.

The ECG frequently displays low voltage of the QRS complexes and diffuse flattening or inversion of the T waves. Atrial fibrillation is present in about one-third of patients. The chest roentgenogram shows a normal or slightly enlarged heart. Pericardial calcification is most common in tuberculous pericarditis. Pericardial calcification may, however, occur in the absence of constriction, and constriction may occur without calcification.

Inasmuch as the usual physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or absent in chronic constrictive pericarditis, hepatic enlargement and dysfunction associated with jaundice and intractable ascites may lead to a mistaken diagnosis of hepatic cirrhosis. This error can be avoided if the neck veins are inspected and found to be distended.

The transthoracic echocardiogram typically shows pericardial thickening, dilation of the inferior vena cava and hepatic veins, and a sharp halt in ventricular filling in early diastole, with normal ventricular systolic function and flattening of the left ventricular posterior wall. There is a distinctive pattern of transvalvular flow velocity on Doppler echocardiography. During inspiration, there is an exaggerated reduction in blood flow

velocity in the pulmonary veins and across the mitral valve and a leftward shift of the ventricular septum; the opposite occurs during expiration. Diastolic flow velocity in the inferior vena cava into the right atrium and across the tricuspid valve increases in an exaggerated manner during inspiration and declines during expiration (Fig. 28-4). However, echocardiography cannot definitively exclude the diagnosis of constrictive pericarditis. CT and MRI scanning (Fig. 28-5) are more accurate than echocardiography in establishing or excluding the presence of a thickened pericardium.

DIFFERENTIAL DIAGNOSIS

Like chronic constrictive pericarditis, cor pulmonale (**Chap. 19**) may be associated with severe systemic venous hypertension but little pulmonary congestion; the heart is usually not enlarged, and a paradoxical pulse may be present. However, in cor pulmonale, advanced parenchymal pulmonary disease is usually apparent and venous pressure falls during inspiration (i.e., Kussmaul's sign is negative). Tricuspid stenosis (**Chap. 23**) may also simulate chronic constrictive pericarditis; congestive hepatomegaly, splenomegaly, ascites, and venous distention may be equally prominent. However, in tricuspid stenosis, a characteristic murmur and the murmur of accompanying mitral stenosis are usually present.

Because constrictive pericarditis can be corrected surgically, it is important to distinguish chronic

constrictive pericarditis from restrictive cardiomyopathy (**Chap. 27**), which has a similar physiologic abnormality (i.e., restriction of ventricular filling). The differentiating features are summarized in Table 28-2. When a patient has progressive, disabling, and unresponsive congestive heart failure and displays any of the features of constrictive heart disease, Doppler echocardiography to record respiratory effects on transvalvular flow and an MRI or CT scan should be obtained to detect or exclude constrictive pericarditis, because the latter is usually correctable.

TREATMENT Constrictive Pericarditis

Pericardial resection is the only definitive treatment of constrictive pericarditis and should be as complete as possible. Dietary sodium restriction and diuretics are useful during preoperative preparation. Coronary arteriography should be carried out preoperatively in patients older than 50 years to exclude unsuspected accompanying coronary artery disease. The benefits derived from cardiac decortication are usually progressive over a period of months. The risk of this operation depends on the extent of penetration of the myocardium by the fibrotic and calcific process, the severity of myocardial atrophy, the extent of secondary impairment of hepatic and/or renal function, and the patient's general condition. Operative mortality is in the range of 5 to 10% even in experienced centers; the patients with the most severe disease are at highest risk. Therefore, surgical treatment should, if possible, be carried out as early as possible in the course.

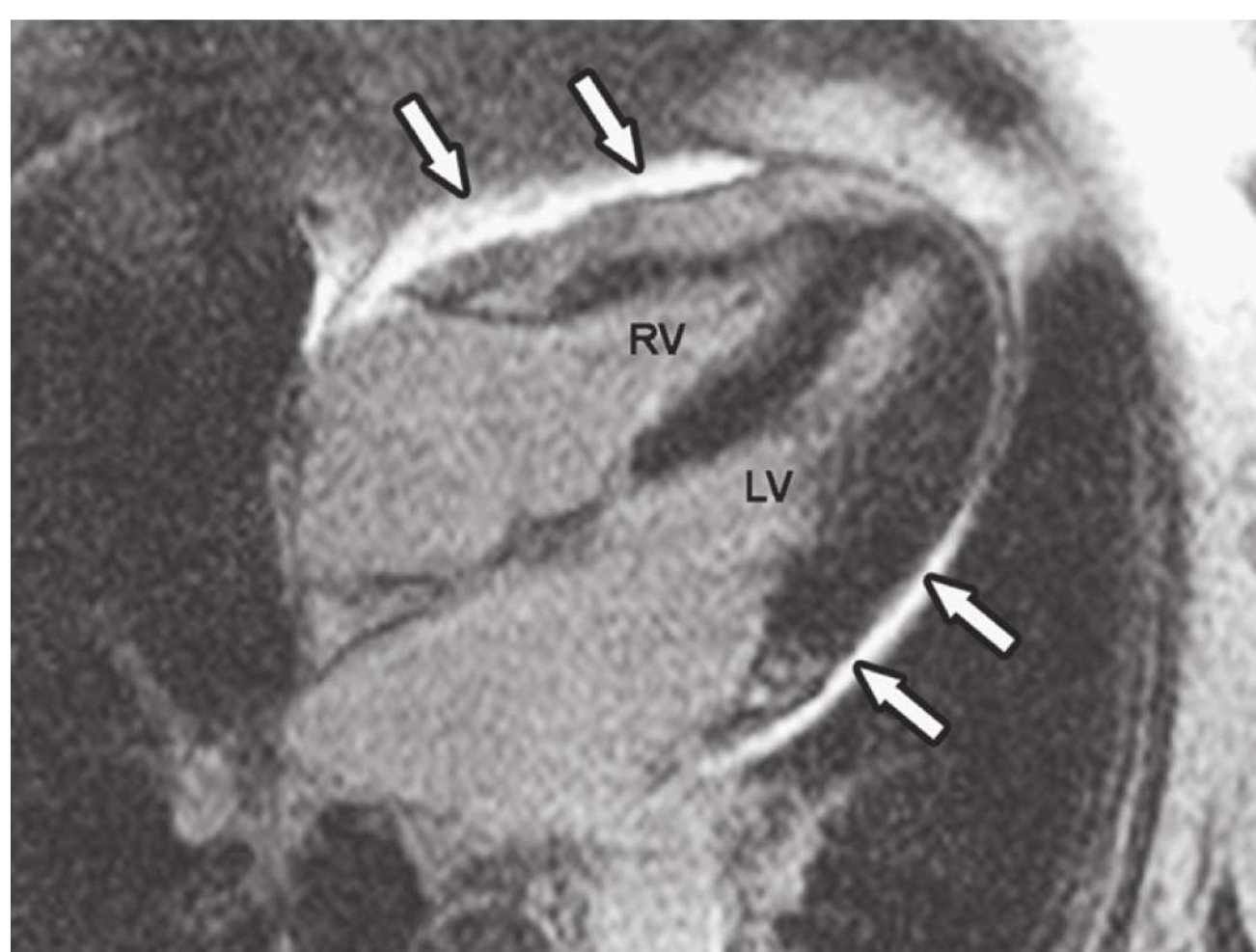


FIGURE 28-5

Magnetic resonance imaging in chronic constrictive pericarditis. The arrows point to a thickened pericardium, which shows late enhancement after gadolinium, characteristic of intense inflammation. LV, left ventricle; RV, right ventricle. (From RY Kwong: Cardiovascular magnetic resonance imaging, in RO Bonow et al [eds]: Braunwald's Heart Disease, 9th ed. Philadelphia: Elsevier, 2012.)

Subacute effusive-constrictive pericarditis

This form of pericardial disease is characterized by the combination of a tense effusion in the pericardial space and constriction of the heart by thickened pericardium. It shares a number of features with both chronic pericardial effusion producing cardiac compression and with pericardial constriction. It may be caused by tuberculosis (see below), multiple attacks of acute idiopathic pericarditis, radiation, traumatic pericarditis, renal failure, scleroderma, and neoplasms. The heart is generally enlarged, and a paradoxical pulse and a prominent x descent (without a prominent y descent) are present in the atrial and jugular venous pressure pulses. After pericardiocentesis, the physiologic findings may change from those of cardiac tamponade to those of pericardial constriction. Furthermore, the intrapericardial pressure and the central venous pressure may decline, but not to normal. The diagnosis can be established by pericardiocentesis followed by pericardial biopsy. Wide excision of both the visceral and parietal pericardium is usually effective therapy.

Tuberculous pericardial disease

Tuberculous infection is a common cause of chronic pericardial effusion, although less so in North America than in the developing world where active tuberculosis is endemic. The clinical picture is that of a chronic, systemic illness in a patient with pericardial effusion. It is important to consider this diagnosis in a patient with known tuberculosis, with HIV, and with fever, chest pain, weight loss, and enlargement of the cardiac silhouette of undetermined origin. If the etiology of chronic pericardial effusion remains obscure despite detailed analysis of the pericardial fluid (see above), a pericardial biopsy, preferably by a limited thoracotomy, should be performed. If definitive evidence is still lacking but the specimen shows granulomas with caseation, antituberculous chemotherapy is indicated.

If the biopsy specimen shows a thickened pericardium after 2–4 weeks of antituberculin therapy, pericardiectomy should be carried out to prevent the development of constriction. Tubercular cardiac

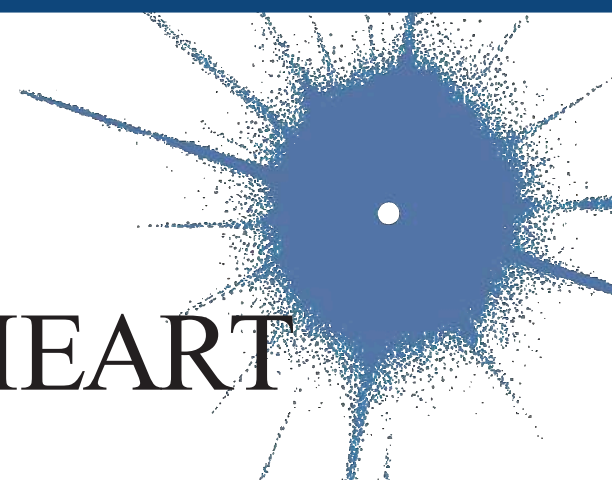
constriction should be treated surgically while the patient is receiving antituberculous chemotherapy.

OTHER DISORDERS OF THE PERICARDIUM

Pericardial cysts appear as rounded or lobulated deformities of the cardiac silhouette, most commonly at the right cardiophrenic angle. They usually do not cause symptoms, and their major clinical significance lies in the possibility of confusion with a tumor, ventricular aneurysm, or massive cardiomegaly. Tumors involving the pericardium are most commonly secondary to malignant neoplasms originating in or invading the mediastinum, including carcinoma of the bronchus and breast, lymphoma, and melanoma. Mesothelioma is the most common primary malignant tumor. The usual clinical picture of malignant pericardial tumor is an insidiously developing, often bloody pericardial effusion. Surgical exploration is required to establish a definitive diagnosis and to carry out definitive or, more commonly, palliative treatment.

CHAPTER 29

TUMORS AND TRAUMA OF THE HEART



Eric H. Awtry ■ Wilson S. Colucci

TUMORS OF THE HEART

PRIMARY TUMORS

Primary tumors of the heart are rare. Approximately three-quarters are histologically benign, and the majority of these tumors are myxomas. Malignant tumors, almost all of which are sarcomas, account for 25% of primary cardiac tumors. All cardiac tumors, regardless of pathologic type, have the potential to cause life-threatening complications. Many tumors are now surgically curable; thus, early diagnosis is imperative.

Clinical presentation

Cardiac tumors may present with a wide array of cardiac and noncardiac manifestations. These manifestations depend in large part on the location and size of the tumor and are often nonspecific features of more common forms of heart disease, such as chest pain, syncope, heart failure, murmurs, arrhythmias, conduction disturbances, and pericardial effusion with or without tamponade. Additionally, embolic phenomena and constitutional symptoms may occur.

Myxoma

Myxomas are the most common type of primary cardiac tumor in adults, accounting for one-third to one-half of all cases at postmortem examination, and about three-quarters of the tumors treated surgically. They occur at all ages, most commonly in the third through sixth decades, with a female predilection. Approximately 90% of myxomas are sporadic; the remainder are familial with autosomal dominant transmission. The familial variety often occurs as part of a syndrome complex (Carney complex) that includes (1) myxomas (cardiac, skin, and/or breast), (2) lentigines and/or pigmented nevi, and (3) endocrine overactivity (primary

nodular adrenal cortical disease with or without Cushing's syndrome, testicular tumors, and/or pituitary adenomas with gigantism or acromegaly). Certain constellations of findings have been referred to as the NAME syndrome (nevi, atrial myxoma, myxoid neurofibroma, and ephelides) or the LAMB syndrome (lentigines, atrial myxoma, and blue nevi), although these syndromes probably represent subsets of the Carney complex. The genetic basis of this complex has not been elucidated completely; however, patients frequently have inactivating mutations in the tumor-suppressor gene *PRKAR1A*, which encodes the protein kinase A type I- α regulatory subunit.

Pathologically, myxomas are gelatinous structures that consist of myxoma cells embedded in a stroma rich in glycosaminoglycans. Most are solitary, arise from the interatrial septum in the vicinity of the fossa ovalis (particularly the left atrium), and are often pedunculated on a fibrovascular stalk. In contrast to sporadic tumors, familial or syndromic tumors tend to occur in younger individuals, are often multiple, may be ventricular in location, and are more likely to recur after initial resection.

Myxomas commonly present with obstructive signs and symptoms. The most common clinical presentation mimics that of mitral valve disease: either stenosis owing to tumor prolapse into the mitral orifice or regurgitation resulting from tumor-induced valvular trauma. Ventricular myxomas may cause outflow obstruction similar to that caused by subaortic or subpulmonic stenosis. The symptoms and signs of myxoma may be sudden in onset or positional in nature, owing to the effects of gravity on tumor position. A characteristic low-pitched sound, a "tumor plop," may be appreciated on auscultation during early or mid-diastole and is thought to result from the impact of the tumor against the mitral valve or ventricular wall. Myxomas also may present with peripheral or pulmonary emboli

or with constitutional signs and symptoms, including fever, weight loss, cachexia, malaise, arthralgias, rash, digital clubbing, Raynaud's phenomenon, hypergammaglobulinemia, anemia, polycythemia, leukocytosis, elevated erythrocyte sedimentation rate, thrombocytopenia, and thrombocytosis. These features account for the frequent misdiagnosis of patients with myxomas as having endocarditis, collagen vascular disease, or a paraneoplastic syndrome.

Two-dimensional transthoracic or omniplane transesophageal echocardiography is useful in the diagnosis of cardiac myxoma and allows assessment of tumor size and determination of the site of tumor attachment, both of which are important considerations in the planning

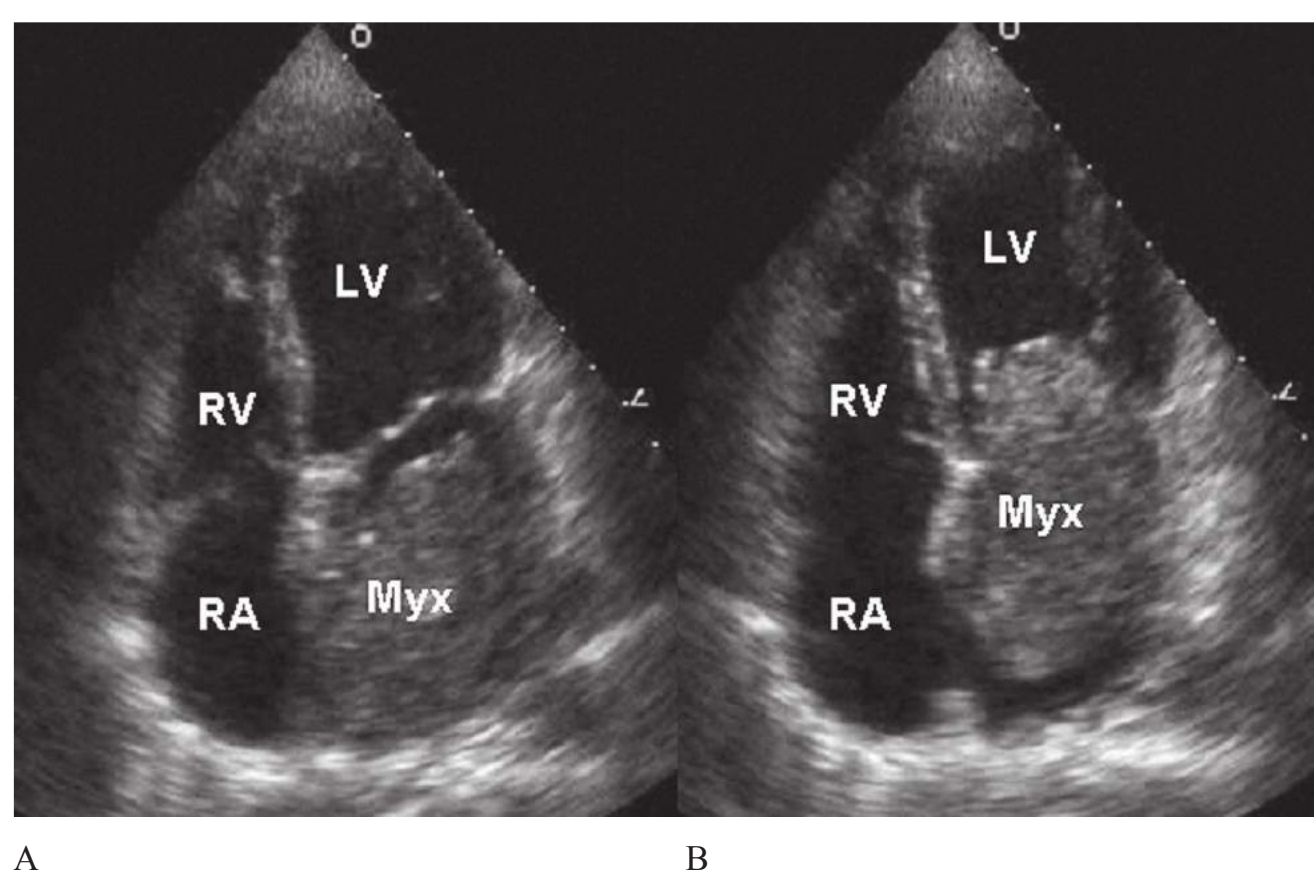


FIGURE 29-1

Transthoracic echocardiogram demonstrating a large atrial myxoma. The myxoma (Myx) fills the entire left atrium in systole (A) and prolapses across the mitral valve and into the left ventricle (LV) during diastole (B). RA, right atrium; RV, right ventricle. (Courtesy of Dr. Michael Tsang; with permission.)

of surgical excision (**Fig. 29-1**). Computed tomography (CT) and magnetic resonance imaging (MRI) may provide important information regarding size, shape, composition, and surface characteristics of the tumor (**Fig. 29-2**).

Although cardiac catheterization and angiography were previously performed routinely before tumor resection, they no longer are considered mandatory when adequate noninvasive information is available and other cardiac disorders (e.g., coronary artery disease) are not considered likely. Additionally, catheterization of the chamber from which the tumor arises carries the risk of tumor embolization. Because myxomas may be familial, echocardiographic screening of first-degree relatives is appropriate, particularly if the patient is young and has multiple tumors or evidence of myxoma syndrome.

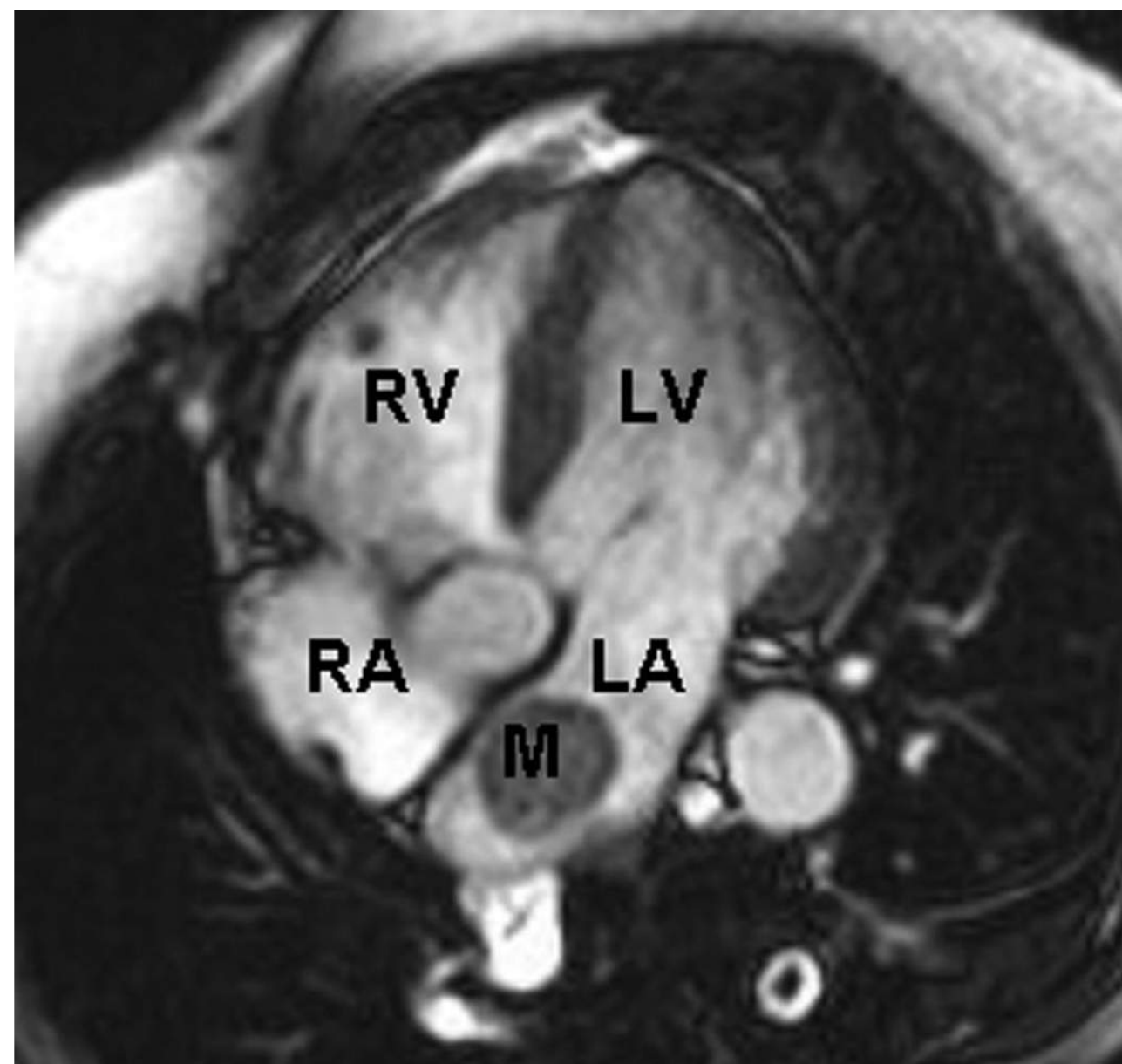


FIGURE 29-2

Cardiac magnetic resonance imaging demonstrating a rounded mass (M) within the left atrium (LA). Pathologic evaluation at the time of surgery revealed it to be an atrial myxoma. LV, left ventricle; RA, right atrium; RV, right ventricle.

TREATMENT Myxoma

Surgical excision using cardiopulmonary bypass is indicated regardless of tumor size and is generally curative. Myxomas recur in 12–22% of familial cases but in only 1–2% of sporadic cases. Tumor recurrence most likely is due to multifocal lesions in the former and inadequate resection in the latter.

Other benign tumors

Cardiac lipomas, although relatively common, are usually incidental findings at postmortem examination; however, they may grow as large as 15 cm and may present with symptoms owing to mechanical interference with cardiac function, arrhythmias, or conduction disturbances or as an abnormality of the cardiac silhouette on chest x-ray. Papillary fibroelastomas are the most common tumors of the cardiac valves. Although usually clinically silent, they can cause valve dysfunction and may embolize distally, resulting in transient ischemic attacks, stroke, or myocardial infarction. In general, these tumors should be resected even when asymptomatic, although a more conservative approach may be considered for small, right-sided lesions. Rhabdomyomas and fibromas are the most common cardiac tumors in infants and children and usually occur in the ventricles, where they may produce mechanical obstruction to blood flow, thereby mimicking valvular stenosis, congestive heart failure (CHF), restrictive or

hypertrophic cardiomyopathy, or pericardial constriction. Rhabdomyomas are probably hamartomatous growths, are multiple in 90% of cases, and are strongly associated with tuberous sclerosis. These tumors have a tendency to regress completely or partially; only tumors that cause obstruction require surgical resection. Fibromas are usually single, are often calcified, tend to grow and cause obstructive symptoms, and should be resected. Hemangiomas and mesotheliomas are generally small tumors, most often intramyocardial in location, and may cause atrioventricular (AV) conduction disturbances and even sudden death as a result of their propensity to develop in the region of the AV node. Other benign tumors arising from the heart include teratoma, chemodectoma, neurilemoma, granular cell myoblastoma, and bronchogenic cysts.

Sarcoma

Almost all malignant primary cardiac tumors are sarcomas, which may be of several histologic types. In general, these tumors are characterized by rapid progression that culminates in the patient's death within weeks to months from the time of presentation as a result of hemodynamic compromise, local invasion, or distant metastases. Sarcomas commonly involve the right side of the heart, are characterized by rapid growth, frequently invade the pericardial space, and may obstruct the cardiac chambers or venae cavae. Sarcomas also may occur on the left side of the heart and may be mistaken for myxomas.

TREATMENT Sarcoma

At the time of presentation, these tumors have often spread too extensively to allow for surgical excision. Although there are scattered reports of palliation with surgery, radiotherapy, and/or chemotherapy, the response of cardiac sarcomas to these therapies is generally poor. The one exception appears to be cardiac lymphosarcomas, which may respond to a combination of chemo- and radiotherapy.

TUMORS METASTATIC TO THE HEART

Tumors metastatic to the heart are much more common than primary tumors, and their incidence is likely to increase as the life expectancy of patients with various forms of malignant neoplasms is extended by more effective therapy. Although cardiac metastases may occur with any tumor type, the relative incidence is especially high in malignant melanoma and, to a somewhat lesser extent, leukemia and lymphoma. In absolute terms, the most common primary originating sites of cardiac metastases are carcinoma of the breast and

lung, reflecting the high incidence of those cancers. Cardiac metastases almost always occur in the setting of widespread primary disease, and most often there is either primary or metastatic disease elsewhere in the thoracic cavity. Nevertheless, cardiac metastasis occasionally may be the initial presentation of an extrathoracic tumor.

Cardiac metastases may occur via hematogenous or lymphangitic spread or by direct tumor invasion. They generally manifest as small, firm nodules; diffuse infiltration also may occur, especially with sarcomas or hematologic neoplasms. The pericardium is most often involved, followed by myocardial involvement of any chamber and, rarely, by involvement of the endocardium or cardiac valves.

Cardiac metastases are clinically apparent only ~10% of the time, are usually not the cause of the patient's presentation, and rarely are the cause of death. The vast majority occur in the setting of a previously recognized malignant neoplasm. As with primary cardiac tumors, the clinical presentation reflects more the location and size of the tumor than its histologic type. When symptomatic, cardiac metastases may result in a variety of clinical features, including dyspnea, acute pericarditis, cardiac tamponade, ectopic tachyarrhythmias, heart block, and CHF. Importantly, many of these signs and symptoms may also result from myocarditis, pericarditis, or cardiomyopathy induced by radiotherapy or chemotherapy.

Electrocardiographic (ECG) findings are nonspecific. On chest x-ray, the cardiac silhouette is most often normal but may be enlarged or exhibit a bizarre contour. Echocardiography is useful for identifying pericardial effusions and visualizing larger metastases, although CT and radionuclide imaging with gallium or thallium may define the tumor burden more clearly. Cardiac MRI offers superb image quality and plays a central role in the diagnostic evaluation of cardiac metastases and cardiac tumors in general. Pericardiocentesis may allow for a specific cytologic diagnosis in patients with malignant pericardial effusions. Angiography is rarely necessary but may delineate discrete lesions.

TREATMENT Tumors Metastatic to the Heart

Most patients with cardiac metastases have advanced malignant disease; thus, therapy is generally palliative and consists of treatment of the primary tumor. Symptomatic malignant pericardial effusions should be drained by pericardiocentesis. Concomitant instillation of a sclerosing agent (e.g., tetracycline or bleomycin) may delay or prevent reaccumulation of the effusion, and creation of a pericardial window allows drainage of the effusion to the pleural or peritoneal space.

Traumatic cardiac injury may be caused by either penetrating or nonpenetrating trauma. Penetrating injuries most often result from gunshot or knife wounds, and the site of entry is usually obvious. Nonpenetrating injuries most often occur during motor vehicle accidents, either from rapid deceleration or from impact of the chest against the steering wheel, and may be associated with significant cardiac injury even in the absence of external signs of thoracic trauma.

NONPENETRATING CARDIAC INJURY

Myocardial contusions are the most common form of nonpenetrating cardiac injury and may initially be overlooked in trauma patients as the clinical focus is directed toward other, more obvious injuries. Myocardial necrosis may occur as a direct result of the blunt injury or as a result of traumatic coronary laceration or thrombosis. The contused myocardium is pathologically similar to infarcted myocardium and may be associated with atrial or ventricular arrhythmias; conduction disturbances, including bundle branch block; or ECG abnormalities resembling those of infarction or pericarditis. Thus, it is important to consider contusion as a cause of otherwise unexplained ECG changes in a trauma patient. Serum creatine kinase, myocardial band (CK-MB) isoenzyme levels are increased in ~20% of patients who experience blunt chest trauma but may be falsely elevated in the presence of massive skeletal muscle injury. Cardiac troponin levels are more specific for identifying cardiac injury in this setting. Echocardiography is useful in detecting structural and functional sequelae of contusion, including wall motion abnormalities (most commonly involving the right ventricle, interventricular septum, or left ventricular apex), pericardial effusion, valvular dysfunction, and ventricular rupture.

Rupture of the cardiac valves or their supporting structures, most commonly of the tricuspid or mitral valve, leads to acute valvular incompetence. This complication is usually heralded by the development of a loud murmur, may be associated with rapidly progressive heart failure, and can be diagnosed by either trans-thoracic or transesophageal echocardiography.

The most serious consequence of nonpenetrating cardiac injury is myocardial rupture, which may result in hemopericardium and tamponade (free wall rupture) or intracardiac shunting (ventricular septal rupture). Although it generally is fatal, up to 40% of patients with cardiac rupture have been reported to survive long enough to reach a specialized trauma center. Hemopericardium also may result from traumatic rupture of a pericardial vessel or a coronary artery. Additionally, a pericardial effusion may develop weeks or even months

after blunt chest trauma as a manifestation of the post-cardiac injury syndrome, which resembles the postpericardiotomy syndrome (**Chap. 28**).

Blunt, nonpenetrating, often innocent-appearing injuries to the chest may trigger ventricular fibrillation even in absence of overt signs of injury. This syndrome, referred to as commotio cordis, occurs most often in adolescents during sporting events (e.g., baseball, hockey, football, and lacrosse) and probably results from an impact to the chest wall overlying the heart during the susceptible phase of repolarization just before the peak of the T wave. Survival depends on prompt defibrillation. Sudden emotional or physical trauma, even in the absence of direct cardiac trauma, may precipitate a transient catecholamine-mediated cardiomyopathy referred to as tako-tsubo syndrome or the apical ballooning syndrome (**Chap. 27**).

Rupture or transection of the aorta, usually just above the aortic valve or at the site of the ligamentum arteriosum, is a common consequence of nonpenetrating chest trauma and is the most common vascular deceleration injury. The clinical presentation is similar to that of aortic dissection (**Chap. 46**); the arterial pressure and pulse amplitude may be increased in the upper extremities and decreased in the lower extremities, and chest x-ray may reveal mediastinal widening. Occasionally, aortic rupture is contained by the aortic adventitia, resulting in a false, or pseudo-, aneurysm that may be discovered months or years after the initial injury.

PENETRATING CARDIAC INJURY

Penetrating injuries of the heart produced by knife or bullet wounds usually result in rapid clinical deterioration and frequently in death as a result of hemopericardium/pericardial tamponade or massive hemorrhage. Nonetheless, up to half of such patients may survive long enough to reach a specialized trauma center if immediate resuscitation is performed. Prognosis in these patients relates to the mechanism of injury, their clinical condition at presentation, and the specific cardiac chamber(s) involved. Iatrogenic cardiac or coronary arterial perforation may complicate placement of central venous or intracardiac catheters, pacemaker leads, or intracoronary stents and is associated with a better prognosis than are other forms of penetrating cardiac trauma.

Traumatic rupture of a great vessel from penetrating injury is usually associated with hemothorax and, less often, hemopericardium. Local hematoma formation may compress major vessels and produce ischemic symptoms, and AV fistulas may develop, occasionally resulting in high-output CHF.

Occasionally, patients who survive penetrating cardiac injuries may subsequently present with a new cardiac murmur or CHF as a result of mitral regurgitation or an

intracardiac shunt (i.e., ventricular or atrial septal defect, aortopulmonary fistula, or coronary AV fistula) that was undetected at the time of the initial injury or developed subsequently. Therefore, trauma patients should be examined carefully several weeks after the injury. If a mechanical complication is suspected, it can be confirmed by echocardiography or cardiac catheterization.

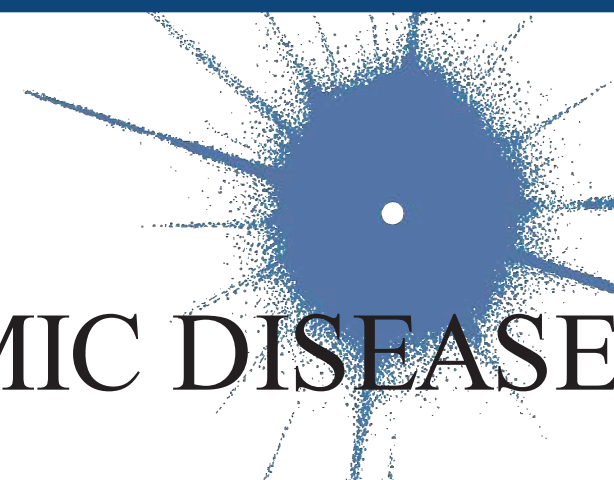
TREATMENT Traumatic Cardiac Injury

The treatment of an uncomplicated myocardial contusion is similar to the medical therapy for a myocardial infarction,

except that anticoagulation is contraindicated, and should include monitoring for the development of arrhythmias and mechanical complications such as cardiac rupture (**Chap. 41**). Acute myocardial failure resulting from traumatic valve rupture usually requires urgent operative correction. Immediate thoracotomy should be carried out for most cases of penetrating injury, or if there is evidence of cardiac tamponade and/or shock regardless of the type of trauma. Pericardiocentesis may be lifesaving in patients with tamponade but is usually only a temporizing measure while awaiting definitive surgical therapy. Pericardial hemorrhage often leads to constriction (**Chap. 28**), which must be treated by surgical decortication.

CHAPTER 30

CARDIAC MANIFESTATIONS OF SYSTEMIC DISEASE



Eric H. Awtry ■ Wilson S. Colucci

The common systemic disorders that have associated cardiac manifestations are summarized in [Table 30-1](#).

DIABETES MELLITUS

Diabetes mellitus, both insulin- and non-insulin-dependent, is an independent risk factor for coronary artery disease (CAD; **Chap. 36**) and accounts for 14–50% of new cases of cardiovascular disease. Furthermore, CAD is the most common cause of death in adults with diabetes mellitus. In the diabetic population, the incidence of CAD relates to the duration of diabetes and the level of glycemic control, and its pathogenesis involves endothelial dysfunction, increased lipoprotein peroxidation, increased inflammation, a prothrombotic state, and associated metabolic abnormalities.

Compared to their nondiabetic counterparts, diabetic patients are more likely to have a myocardial infarction, have a greater burden of CAD, have larger infarct size, and have more postinfarct complications, including heart failure, shock, and death. Importantly, diabetic patients are more likely to have atypical ischemic symptoms; nausea, dyspnea, pulmonary edema, arrhythmias, heart block, or syncope may be their anginal equivalent. Additionally, “silent ischemia,” resulting from autonomic nervous system dysfunction, is more common in diabetic patients, accounting for up to 90% of their ischemic episodes. Thus, one must have a low threshold for suspecting CAD in diabetic patients. The treatment of diabetic patients with CAD must include aggressive risk factor management. Considerations regarding pharmacologic therapy and revascularization strategies are similar in diabetic and nondiabetic patients except that diabetic patients have higher morbidity and mortality rates associated with revascularization, have an increased risk of restenosis after percutaneous coronary intervention (PCI), and have improved survival when treated with surgical bypass compared with PCI for multivessel CAD.

Patients with diabetes mellitus also may have abnormal left ventricular systolic and diastolic function, reflecting concomitant epicardial CAD and/or hypertension, coronary microvascular disease, endothelial dysfunction, ventricular hypertrophy, and autonomic dysfunction. Furthermore, the increase in intramyocardial lipid deposition (predominantly nonesterified fatty acids) that is characteristic of diabetic states may contribute to both systolic and diastolic dysfunction by impairing insulin signaling, reducing trans-sarcolemma calcium flux, and inducing myocyte apoptosis. A restrictive cardiomyopathy may be present with abnormal myocardial relaxation and elevated ventricular filling pressures. Histologically, interstitial fibrosis is seen, and intramural arteries may demonstrate intimal thickening, hyaline deposition, and inflammatory changes. Diabetic patients have an increased risk of developing clinical heart failure, which probably contributes to their excessive cardiovascular morbidity and mortality rates. There is some evidence that insulin therapy may ameliorate diabetes-related myocardial dysfunction.

MALNUTRITION AND VITAMIN DEFICIENCY

Malnutrition

In patients whose intake of protein, calories, or both is severely deficient, the heart may become thin, pale, and hypokinetic with myofibrillar atrophy and interstitial edema. The systolic pressure and cardiac output fall, and the pulse pressure narrows. Generalized edema is common and relates to a variety of factors, including reduced serum oncotic pressure and myocardial dysfunction. Such profound states of protein and calorie malnutrition, termed kwashiorkor and marasmus, respectively, are most common in underdeveloped countries. However, significant nutritional heart disease also may occur in developed nations, particularly

TABLE 30-1

COMMON SYSTEMIC DISORDERS AND THEIR ASSOCIATED CARDIAC MANIFESTATIONS		
SYSTEMIC DISORDER	COMMON CARDIAC MANIFESTATIONS	CHAPTER ^a
Diabetes mellitus	CAD, atypical angina, CMP, systolic or diastolic CHF	417
Protein-calorie malnutrition	Dilated CMP, CHF	97
Thiamine deficiency	High-output failure, dilated CMP	96e
Hyperhomocysteinemia	Premature atherosclerosis	96e
Obesity	CMP, systolic or diastolic CHF	415e
Hyperthyroidism	Palpitations, SVT, atrial fibrillation, hypertension	405
Hypothyroidism	Hypotension, bradycardia, dilated CMP, CHF, pericardial effusion	405
Malignant carcinoid	Tricuspid and pulmonary valve disease, right heart failure	113
Pheochromocytoma	Hypertension, palpitations, CHF	407
Acromegaly	Systolic or diastolic heart failure	401e
Rheumatoid arthritis	Pericarditis, pericardial effusions, coronary arteritis, myocarditis, valvulitis	380
Seronegative arthropathies	Aortitis, aortic and mitral insufficiency, conduction abnormalities	384
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, myocarditis, arterial and venous thrombosis	378
HIV	Myocarditis, dilated CMP, pericardial effusion	226
Amyloidosis	CHF, restrictive CMP, valvular regurgitation, pericardial effusion	137
Sarcoidosis	CHF, dilated or restrictive CMP, ventricular arrhythmias, heart block	390
Hemochromatosis	CHF, arrhythmias, heart block	428
Marfan syndrome	Aortic aneurysm and dissection, aortic insufficiency, mitral valve prolapse	427
Ehlers-Danlos syndrome	Aortic and coronary aneurysms, mitral and tricuspid valve prolapse	427
Systemic sclerosis	Pericardial effusion, CHF (systolic and diastolic), myocarditis, coronary microvascular vasospasm, tachyarrhythmias	382

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CMP, cardiomyopathy; SVT, supraventricular tachycardia.

^aFrom Kasper DL, Hauser SL, Jameson JL, Anthony SF, Longo DL, Loscalzo J (eds). *Harrison's Principles of Internal Medicine*, 19th ed. New York, McGraw-Hill, 2016, ISBN 978-0-07-180215-4.

in patients with chronic diseases such as AIDS, patients with anorexia nervosa, and patients with severe cardiac failure in whom gastrointestinal hypoperfusion and venous congestion may lead to anorexia and malabsorption. Open-heart surgery poses increased risk in malnourished patients; such patients may benefit from preoperative hyperalimentation.

Thiamine deficiency (Beriberi)

Generalized malnutrition often is accompanied by thiamine deficiency; however, this hypovitaminosis also may occur in the presence of an adequate protein and caloric intake, particularly in East Asia, where polished rice deficient in thiamine may be a major dietary component. In Western nations where the use of thiamine-enriched flour is widespread, clinical thiamine deficiency is limited primarily to alcoholics, food faddists, and patients receiving chemotherapy. Nonetheless, when thiamine stores are measured using the thiamine-pyrophosphate effect (TPPE), thiamine deficiency has been found in 20–90% of patients with chronic heart failure. This deficiency appears to

result from both reduced dietary intake and a diuretic-induced increase in the urinary excretion of thiamine. The acute administration of thiamine to these patients increases the left ventricular ejection fraction and the excretion of salt and water.

Clinically, patients with thiamine deficiency usually have evidence of generalized malnutrition, peripheral neuropathy, glossitis, and anemia. The classic associated cardiovascular syndrome is characterized by high-output heart failure, tachycardia, and often elevated biventricular filling pressures. The major cause of the high-output state is vasomotor depression leading to reduced systemic vascular resistance, the precise mechanism of which is not understood. The cardiac examination may reveal a wide pulse pressure, tachycardia, a third heart sound, and an apical systolic murmur. The electrocardiogram (ECG) may reveal decreased voltage, a prolonged QT interval, and T-wave abnormalities. The chest x-ray generally reveals cardiomegaly and signs of congestive heart failure (CHF). The response to thiamine is often dramatic, with an increase in systemic vascular resistance, a decrease in cardiac output, clearing of pulmonary congestion, and a reduction in heart

size often occurring in 12–48 h. Although the response to inotropes and diuretics may be poor before thiamine therapy, these agents may be important after thiamine repletion, since the left ventricle may not be able to handle the increased work load presented by the return of vascular tone.

Vitamin B₆, B₁₂, and folate deficiency

Vitamin B₆, vitamin B₁₂, and folate are cofactors in the metabolism of homocysteine. Their deficiency probably contributes to the majority of cases of hyperhomocysteinemia, a disorder associated with increased atherosclerotic risk. Supplementation of these vitamins has reduced the incidence of hyperhomocysteinemia in the United States; however, the clinical cardiovascular benefit of normalizing elevated homocysteine levels has not been proved.

OBESITY

Obesity is associated with an increased prevalence of hypertension, glucose intolerance, atherosclerotic CAD, atrial fibrillation, obstructive sleep apnea, and pulmonary hypertension, and is associated with increased cardiovascular morbidity and mortality rates. In addition, obese patients have a distinct hemodynamic profile characterized by increased total and central blood volumes, increased cardiac output, and elevated left ventricular filling pressure. The elevated cardiac output appears to be required to support the metabolic demands of the excess adipose tissue. Left ventricular filling pressure is often at the upper limits of normal at rest and rises excessively with exercise, contributing to exertional dyspnea. In part as a result of chronic volume overload, eccentric cardiac hypertrophy with cardiac dilation and ventricular diastolic and/or systolic dysfunction may develop. In addition, altered levels of adipokines secreted by adipose tissue may contribute to adverse myocardial remodeling via direct effects on cardiac myocytes and other cells. Pathologically, there is left and, in some cases, right ventricular hypertrophy and generalized cardiac dilation. Pulmonary congestion, peripheral edema, and exercise intolerance may all ensue; however, the recognition of these findings may be difficult in massively obese patients.

Treatment with angiotensin-converting enzyme inhibitors, sodium restriction, and diuretics may be useful to control heart failure symptoms. Weight reduction, however, is the most effective therapy and results in reduction in blood volume and the return of cardiac output toward normal. However, rapid weight reduction may be dangerous, as cardiac arrhythmias and sudden death owing to electrolyte imbalance have been described.

THYROID DISEASE

Thyroid hormone exerts a major influence on the cardiovascular system by a number of direct and indirect mechanisms, and not surprisingly, cardiovascular effects are prominent in both hypo- and hyperthyroidism. Thyroid hormone causes increases in total-body metabolism and oxygen consumption that indirectly increase the cardiac workload. In addition, thyroid hormone exerts direct inotropic, chronotropic, and dromotropic effects that are similar to those seen with adrenergic stimulation (e.g., tachycardia, increased cardiac output); they are mediated at least partly by both transcriptional and nontranscriptional effects of thyroid hormone on myosin, calcium-activated ATPase, Na⁺-K⁺-ATPase, and myocardial β -adrenergic receptors.

Hyperthyroidism

Common cardiovascular manifestations of hyperthyroidism include palpitations, systolic hypertension, and fatigue. Sinus tachycardia is present in ~40% of hyperthyroid patients, and atrial fibrillation is present in ~15%. Physical examination may reveal a hyperdynamic precordium, a widened pulse pressure, increases in the intensity of the first heart sound and the pulmonic component of the second heart sound, and a third heart sound. An increased incidence of mitral valve prolapse has been described in hyperthyroid patients, in which case a midsystolic murmur may be heard at the left sternal border with or without a midsystolic click. A systolic pleuropericardial friction rub (Means-Lerman scratch) may be heard at the left second intercostal space during expiration and is thought to result from the hyperdynamic cardiac motion.

Elderly patients with hyperthyroidism may present with only cardiovascular manifestations of thyrotoxicosis such as sinus tachycardia, atrial fibrillation, and hypertension, all of which may be resistant to therapy until the hyperthyroidism is controlled. Angina pectoris and CHF are unusual with hyperthyroidism unless there is coexistent heart disease; in such cases, symptoms often resolve with treatment of the hyperthyroidism.

Hypothyroidism

Cardiac manifestations of hypothyroidism include a reduction in cardiac output, stroke volume, heart rate, systolic blood pressure, and pulse pressure. Pericardial effusions are present in about one-third of patients, rarely progress to tamponade, and probably result from increased capillary permeability. Other clinical signs include cardiomegaly, bradycardia, weak arterial pulses, distant heart sounds, and pleural effusions. Although the signs and symptoms of myxedema may

mimic those of CHF, in the absence of other cardiac disease, myocardial failure is uncommon. The ECG generally reveals sinus bradycardia and low voltage and may show prolongation of the QT interval, decreased P-wave voltage, prolonged AV conduction time, intraventricular conduction disturbances, and nonspecific ST-T-wave abnormalities. Chest x-ray may show cardiomegaly, often with a “water bottle” configuration; pleural effusions; and, in some cases, evidence of CHF. Pathologically, the heart is pale and dilated and often demonstrates myofibrillar swelling, loss of striations, and interstitial fibrosis.

Patients with hypothyroidism frequently have elevations of cholesterol and triglycerides, resulting in premature atherosclerotic CAD. Before treatment with thyroid hormone, patients with hypothyroidism frequently do not have angina pectoris, presumably because of the low metabolic demands caused by their condition. However, angina and myocardial infarction may be precipitated during initiation of thyroid hormone replacement, especially in elderly patients with underlying heart disease. Therefore, replacement should be done with care, starting with low doses that are increased gradually.

MALIGNANT CARCINOID

Carcinoid tumors most often originate in the small bowel and elaborate a variety of vasoactive amines (e.g., serotonin), kinins, indoles, and prostaglandins that are believed to be responsible for the diarrhea, flushing, and labile blood pressure that characterize the carcinoid syndrome. Some 50% of patients with carcinoid syndrome have cardiac involvement, usually manifesting as abnormalities of the tricuspid or pulmonic valves. These patients invariably have hepatic metastases that allow vasoactive substances to circumvent hepatic metabolism. Left-sided cardiac involvement is rare and indicates either pulmonary carcinoid or an intracardiac shunt. Pathologically, carcinoid lesions are fibrous plaques that consist of smooth-muscle cells embedded in a stroma of glycosaminoglycans and collagen. They occur on the cardiac valves, where they cause valvular dysfunction, as well as on the endothelium of the cardiac chambers and great vessels.

Carcinoid heart disease most often presents as tricuspid regurgitation, pulmonic stenosis, or both. In some cases, a high cardiac output state may occur, presumably as a result of a decrease in systemic vascular resistance resulting from vasoactive substances released by the tumor. Treatment with somatostatin analogues (e.g., octreotide) or interferon α improves symptoms and survival in patients with carcinoid heart disease but does not appear to improve valvular abnormalities. Treatment with diuretics usually mitigates the symptoms

of right heart failure; in some severely symptomatic patients, valve replacement is indicated. Coronary artery spasm, presumably due to a circulating vasoactive substance, may occur in patients with carcinoid syndrome.

PHEOCHROMOCYTOMA

In addition to causing labile or sustained hypertension, the high circulating levels of catecholamines resulting from a pheochromocytoma may cause direct myocardial injury. Focal myocardial necrosis and inflammatory cell infiltration are present in ~50% of patients who die with pheochromocytoma and may contribute to clinically significant left ventricular failure and pulmonary edema. In addition, associated hypertension results in left ventricular hypertrophy. Left ventricular dysfunction and CHF may resolve after removal of the tumor.

ACROMEGALY

Exposure of the heart to excessive growth hormone may cause CHF as a result of high cardiac output, diastolic dysfunction owing to ventricular hypertrophy (with increased left ventricular chamber size or wall thickness), or global systolic dysfunction. Hypertension occurs in up to one-third of patients with acromegaly and is characterized by suppression of the renin-angiotensin-aldosterone axis and increases in total-body sodium and plasma volume. Some form of cardiac disease occurs in about one-third of patients with acromegaly and is associated with a doubling of the risk of cardiac death.

RHEUMATOID ARTHRITIS AND THE COLLAGEN VASCULAR DISEASES

Rheumatoid arthritis

Rheumatoid arthritis may be associated with inflammatory changes in any or all cardiac structures, although pericarditis is the most common clinical entity. Pericardial effusions are found on echocardiography in 10–50% of patients with rheumatoid arthritis, particularly those with subcutaneous nodules. Nonetheless, only a small fraction of these patients have symptomatic pericarditis, and when present, it usually follows a benign course, only occasionally progressing to cardiac tamponade or constrictive pericarditis. The pericardial fluid is generally exudative, with decreased concentrations of complement and glucose and elevated cholesterol. Coronary arteritis with intimal inflammation and edema is present in ~20% of cases but only rarely results in angina pectoris or myocardial infarction. Inflammation and granuloma formation may affect the cardiac

valves, most often the mitral and aortic valves, and may cause clinically significant regurgitation owing to valve deformity. Myocarditis is uncommon and rarely results in cardiac dysfunction.

Treatment is directed at the underlying rheumatoid arthritis and may include glucocorticoids. Urgent pericardiocentesis should be performed in patients with tamponade, but pericardiectomy usually is required in cases of pericardial constriction.

Seronegative arthropathies

The seronegative arthropathies, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and the arthritides associated with ulcerative colitis and regional enteritis, are all strongly associated with the HLA-B27 histocompatibility antigen and may be accompanied by a pancarditis and proximal aortitis. The aortic inflammation usually is limited to the aortic root but may extend to involve the aortic valve, mitral valve, and ventricular myocardium, resulting in aortic and mitral regurgitation, conduction abnormalities, and ventricular dysfunction. One-tenth of these patients have significant aortic insufficiency, and one-third have conduction disturbances; both are more common in patients with peripheral joint involvement and longstanding disease. Treatment with aortic valve replacement and permanent pacemaker implantation may be required. Occasionally, aortic regurgitation precedes the onset of arthritis, and therefore, the diagnosis of a

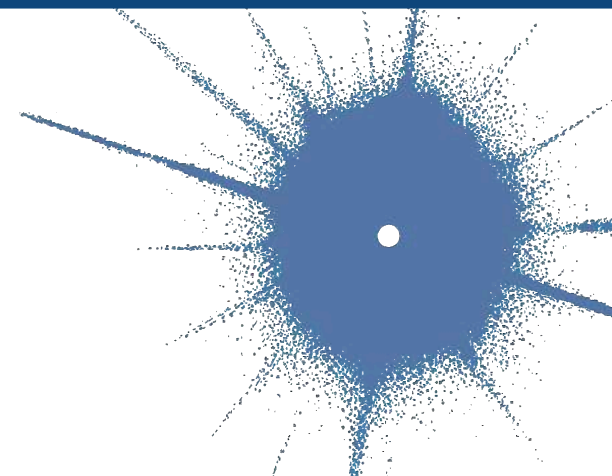
seronegative arthritis should be considered in young males with isolated aortic regurgitation.

Systemic lupus erythematosus (SLE)

A significant percentage of patients with SLE have cardiac involvement. Pericarditis is common, occurring in about two-thirds of patients, and generally follows a benign course, although rarely tamponade or constriction may result. The characteristic endocardial lesions of SLE are verrucous valvular abnormalities known as Libman-Sacks endocarditis. They most often are located on the left-sided cardiac valves, particularly on the ventricular surface of the posterior mitral leaflet, and are made up almost entirely of fibrin. These lesions may embolize or become infected but rarely cause hemodynamically important valvular regurgitation. Myocarditis generally parallels the activity of the disease and, although common histologically, seldom results in clinical heart failure unless associated with hypertension. Although arteritis of epicardial coronary arteries may occur, it rarely results in myocardial ischemia. There is, however, an increased incidence of coronary atherosclerosis that probably is related more to associated risk factors and glucocorticoid use than to SLE itself. Patients with the antiphospholipid antibody syndrome may have a higher incidence of cardiovascular abnormalities, including valvular regurgitation, venous and arterial thrombosis, premature stroke, myocardial infarction, pulmonary hypertension, and cardiomyopathy.

CHAPTER 31

INFECTIVE ENDOCARDITIS



Adolf W. Karchmer

The prototypic lesion of infective endocarditis, the vegetation (**Fig. 31-1**), is a mass of platelets, fibrin, microcolonies of microorganisms, and scant inflammatory cells. Infection most commonly involves heart valves but may also occur on the low-pressure side of a ventricular septal defect, on mural endocardium damaged by aberrant jets of blood or foreign bodies, or on intracardiac devices themselves. The analogous process involving arteriovenous shunts, arterio-arterial shunts (patent ductus arteriosus), or a coarctation of the aorta is called infective endarteritis.

Endocarditis can be classified according to the temporal evolution of disease, the site of infection, the cause of infection, or the predisposing risk factor (e.g., injection drug use). While each classification criterion provides therapeutic and prognostic insight, none is sufficient alone. Acute endocarditis is a hectically febrile illness that rapidly damages cardiac structures, seeds extracardiac sites, and, if untreated, progresses to death within weeks. Subacute endocarditis follows an indolent course; causes structural cardiac damage only slowly, if at all; rarely metastasizes; and is gradually progressive unless complicated by a major embolic event or a ruptured mycotic aneurysm.

In developed countries, the incidence of endocarditis ranges from 4 to 7 cases per 100,000 population per year and has remained relatively stable during recent decades. While congenital heart diseases remain a constant predisposition, predisposing conditions in developed countries have shifted from chronic rheumatic heart disease (still a common predisposition in developing countries) to illicit IV drug use, degenerative valve disease, and intracardiac devices. The incidence of endocarditis is notably increased among the elderly. In developed countries, 25–35% of cases of native valve endocarditis (NVE) are associated with health care, and 16–30% of all cases of endocarditis involve prosthetic valves. The risk of prosthesis infection is greatest during the first 6–12 months after valve replacement; gradually

declines to a low, stable rate thereafter; and is similar for mechanical and bioprosthetic devices. The incidence of endocarditis involving cardiovascular implantable electronic devices (CIED), primarily permanent pacemakers and implantable cardioverter-defibrillators, ranges from 0.5 to 1.14 cases per 1000 device recipients and is higher among patients with an implantable cardioverter-defibrillator than among those with a permanent pacemaker.

ETIOLOGY

Although many species of bacteria and fungi cause sporadic episodes of endocarditis, a few bacterial species cause the majority of cases (**Table 31-1**). The oral cavity, skin, and upper respiratory tract are the respective primary portals for viridans streptococci, staphylococci, and HACEK organisms (*Haemophilus* species, *Aggregatibacter aphrophilus*, *A. actinomycetemcomitans*, *Cardiobacterium* species, *Eikenella* species, and *Kingella* species). *Streptococcus gallolyticus* subspecies *gallolyticus* (formerly *S. bovis* biotype 1) originates from the gastrointestinal tract, where it is associated with polyps and colonic tumors, and enterococci enter the bloodstream from the genitourinary tract. Health care–associated NVE, most commonly caused by *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci, may have either a nosocomial onset (55%) or a community onset (45%); community-onset cases develop in patients who have had extensive contact with the health care system over the preceding 90 days. Endocarditis complicates 6–25% of episodes of catheter-associated *S. aureus* bacteremia; the higher rates are detected in high-risk patients studied by transesophageal echocardiography (TEE) (see “Echocardiography,” later).

Prosthetic valve endocarditis (PVE) arising within 2 months of valve surgery is generally nosocomial, the result of intraoperative contamination of the prosthesis or a bacteremic postoperative complication. It is

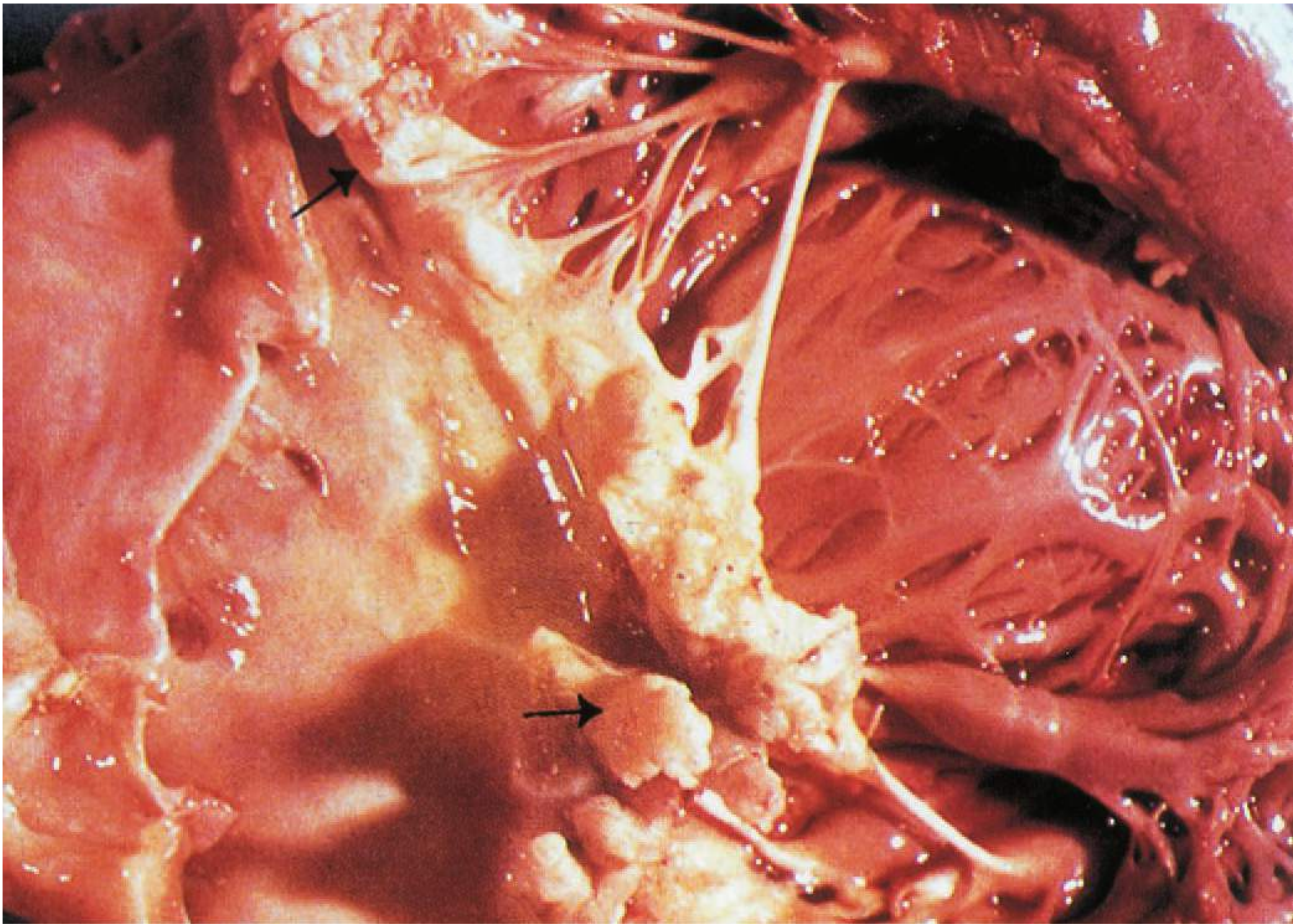


FIGURE 31-1
Vegetations (arrows) due to viridans streptococcal endocarditis involving the mitral valve.

nosocomial origin is reflected in the primary microbial causes: *S. aureus*, CoNS, facultative gram-negative bacilli, diphtheroids, and fungi. The portals of entry and organisms causing cases beginning >12 months after surgery are similar to those in community-acquired NVE. PVE due to CoNS that presents 2–12 months after surgery often represents delayed-onset nosocomial infection. Regardless of the time of onset after surgery, at least 68–85% of CoNS strains that cause PVE are resistant to methicillin.

Endocarditis related to a permanent pacemaker or an implantable cardioverter-defibrillator involves the device or the endothelium at points of device contact. Occasionally, there is concurrent aortic or mitral valve infection. One-third of cases of CIED endocarditis present within 3 months after device implantation or manipulation, one-third present at 4–12 months, and one-third present at >1 year. *S. aureus* and CoNS, both of which are commonly resistant to methicillin, cause the majority of cases.

TABLE 31-1
ORGANISMS CAUSING MAJOR CLINICAL FORMS OF ENDOCARDITIS

ORGANISM	NATIVE VALVE ENDOCARDITIS		PROSTHETIC VALVE ENDOCARDITIS AT INDICATED TIME OF ONSET (MONTHS) AFTER VALVE SURGERY			ENDOCARDITIS IN INJECTION DRUG USERS		
	COMMUNITY-ACQUIRED (N= 1718)	HEALTH CARE-ASSOCIATED (N= 1110)	PERCENTAGE OF CASES			RIGHT-SIDED (N= 346)	LEFT-SIDED (N= 204)	TOTAL (N= 675) ^a
			<2 (N= 144)	2–12 (N= 31)	>12 (N= 194)			
Streptococci ^b	40	13	1	9	31	5	15	12
Pneumococci	2	—	—	—	—	—	—	—
Enterococci ^c	9	16	8	12	11	2	24	9
Staphylococcus aureus	28	52 ^d	22	12	18	77	23	57
Coagulase-negative staphylococci	5	11	33	32	11	—	—	—
Fastidious gram-negative coccobacilli (HACEK group) ^e	3	—	—	—	6	—	—	—
Gram-negative bacilli	1	1	13	3	6	5	13	7
Candida spp.	<1	1	8	12	1	—	12	4
Polymicrobial/miscellaneous	3	3	3	6	5	8	10	7
Diphtheroids	—	<1	6	—	3	—	—	0.1
Culture-negative	9	3	5	6	8	3	3	3

^aThe total number of cases is larger than the sum of right- and left-sided cases because the location of infection was not specified in some cases.

^bIncludes viridans streptococci; *Streptococcus gallolyticus*; other non-group A, groupable streptococci; and *Abiotrophia* and *Granulicatella* spp. (nutritionally variant, pyridoxal-requiring streptococci).

^cPrimarily *E. faecalis* or nonspiciated isolates; occasionally *E. faecium* or other, less likely species.

^dMethicillin resistance is common among these *S. aureus* strains.

^eIncludes *Haemophilus* spp., *Aggregatibacter aphrophilus*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., and *Kingella* spp.

Note: Data are compiled from multiple studies.

Injection drug use–associated endocarditis, especially that involving the tricuspid valve, is commonly caused by *S. aureus*, which in many cases is resistant to methicillin. Left-sided valve infections in addicts have a more varied etiology. In addition to the usual causes of endocarditis, these cases can be due to *Pseudomonas aeruginosa* and *Candida* species, and sporadic cases can be caused by unusual organisms such as *Bacillus*, *Lactobacillus*, and *Corynebacterium* species. Polymicrobial endocarditis occurs among injection drug users. HIV infection in drug users does not significantly influence the causes of endocarditis.

From 5% to 15% of patients with endocarditis have negative blood cultures; in one-third to one-half of these cases, cultures are negative because of prior antibiotic exposure. The remainder of these patients are infected by fastidious organisms, such as nutritionally variant bacteria (now designated *Granulicatella* and *Abiotrophia* species), HACEK organisms, *Coxiella burnetii*, and *Bartonella* species. Some fastidious organisms occur in characteristic geographic settings (e.g., *C. burnetii* and *Bartonella* species in Europe, *Brucella* species in the Middle East). *Tropheryma whippelii* causes an indolent, culture-negative, afebrile form of endocarditis.

PATHOGENESIS

The undamaged endothelium is resistant to infection by most bacteria and to thrombus formation. Endothelial injury (e.g., at the site of impact of high-velocity blood jets or on the low-pressure side of a cardiac structural lesion) allows either direct infection by virulent organisms or the development of a platelet-fibrin thrombus—a condition called nonbacterial thrombotic endocarditis (NBTE). This thrombus serves as a site of bacterial attachment during transient bacteremia. The cardiac conditions most commonly resulting in NBTE are mitral regurgitation, aortic stenosis, aortic regurgitation, ventricular septal defects, and complex congenital heart disease. NBTE also arises as a result of a hypercoagulable state; this gives rise to marantic endocarditis (uninfected vegetations seen in patients with malignancy and chronic diseases) and to bland vegetations complicating systemic lupus erythematosus and the antiphospholipid antibody syndrome.

Organisms that cause endocarditis enter the bloodstream from mucosal surfaces, the skin, or sites of focal infection. Except for more virulent bacteria (e.g., *S. aureus*) that can adhere directly to intact endothelium or exposed subendothelial tissue, microorganisms in the blood adhere at sites of NBTE. The organisms that commonly cause endocarditis have surface adhesin molecules, collectively called microbial surface components recognizing adhesin matrix molecules (MSCRAMMs), that mediate adherence to NBTE sites

or injured endothelium. Adherence is facilitated by fibronectin-binding proteins present on many gram-positive bacteria; by clumping factor (a fibrinogen- and fibrin-binding surface protein) on *S. aureus*; by fibrinogen-binding surface proteins (Fss2), collagen-binding surface protein (Ace), and Ebp pili (the latter mediating platelet adherence) in *Enterococcus faecalis*; and by glucans or FimA (a member of the family of oral mucosal adhesins) on streptococci. Fibronectin-binding proteins are required for *S. aureus* invasion of intact endothelium; thus these surface proteins may facilitate infection of previously normal valves. If resistant to the bactericidal activity of serum and the microbicidal peptides released locally by platelets, adherent organisms proliferate to form dense microcolonies. Microorganisms also induce platelet deposition and a localized procoagulant state by eliciting tissue factor from the endothelium or, in the case of *S. aureus*, from monocytes as well. Fibrin deposition combines with platelet aggregation and microorganism proliferation to generate an infected vegetation. Organisms deep in vegetations are metabolically inactive (nongrowing) and relatively resistant to killing by antimicrobial agents. Proliferating surface organisms are shed into the bloodstream continuously.

The clinical manifestations of endocarditis—other than constitutional symptoms, which probably result from cytokine production—arise from damage to intracardiac structures; embolization of vegetation fragments, leading to infection or infarction of remote tissues; hematogenous infection of sites during bacteremia; and tissue injury due to the deposition of circulating immune complexes or immune responses to deposited bacterial antigens.

CLINICAL MANIFESTATIONS

The clinical endocarditis syndrome is highly variable and spans a continuum between acute and subacute presentations. NVE, PVE, and endocarditis due to injection drug use share clinical and laboratory manifestations (Table 31-2). The causative microorganism is primarily responsible for the temporal course of endocarditis. β -Hemolytic streptococci, *S. aureus*, and pneumococci typically result in an acute course, although *S. aureus* occasionally causes subacute disease. Endocarditis caused by *Staphylococcus lugdunensis* (a coagulase-negative species) or by enterococci may present acutely. Subacute endocarditis is typically caused by viridans streptococci, enterococci, CoNS, and the HACEK group. Endocarditis caused by *Bartonella* species, *T. whippelii*, or *C. burnetii* is exceptionally indolent.

In patients with subacute presentations, fever is typically low-grade and rarely exceeds 39.4°C (103°F); in contrast, temperatures of 39.4–40°C (103–104°F) are

TABLE 31-2

CLINICAL AND LABORATORY FEATURES OF INFECTIVE ENDOCARDITIS	
FEATURE	FREQUENCY, %
Fever	80–90
Chills and sweats	40–75
Anorexia, weight loss, malaise	25–50
Myalgias, arthralgias	15–30
Back pain	7–15
Heart murmur	80–85
New/worsened regurgitant murmur	20–50
Arterial emboli	20–50
Splenomegaly	15–50
Clubbing	10–20
Neurologic manifestations	20–40
Peripheral manifestations (Osler’s nodes, subungual hemorrhages, Janeway lesions, Roth’s spots)	2–15
Petechiae	10–40
Laboratory manifestations	
Anemia	70–90
Leukocytosis	20–30
Microscopic hematuria	30–50
Elevated erythrocyte sedimentation rate	60–90
Elevated C-reactive protein level	>90
Rheumatoid factor	50
Circulating immune complexes	65–100
Decreased serum complement	5–40

often noted in acute endocarditis. Fever may be blunted in patients who are elderly, are severely debilitated, or have renal failure.

Cardiac manifestations

Although heart murmurs are usually indicative of the predisposing cardiac pathology rather than of endocarditis, valvular damage and ruptured chordae may result in new regurgitant murmurs. In acute endocarditis involving a normal valve, murmurs may be absent initially but ultimately are detected in 85% of cases. Congestive heart failure (CHF) develops in 30–40% of patients as a consequence of valvular dysfunction. Occasionally, CHF is due to endocarditis-associated myocarditis or an intracardiac fistula. Heart failure due to aortic valve dysfunction progresses more rapidly than does that due to mitral valve dysfunction. Extension of infection beyond valve leaflets into adjacent annular or myocardial tissue results in perivalvular abscesses, which in turn may cause intracardiac fistulae

with new murmurs. Abscesses may burrow from the aortic valve annulus through the epicardium, causing pericarditis, or into the upper ventricular septum, where they may interrupt the conduction system, leading to varying degrees of heart block. Mitral perivalvular abscesses, which are usually more distant from the conduction system, only rarely cause conduction abnormalities; if such abnormalities occur in this setting, the conduction pathway is most likely disrupted near the atrioventricular node or in the proximal bundle of His. Emboli to a coronary artery occur in 2% of patients and may result in myocardial infarction.

Noncardiac manifestations

The classic nonsuppurative peripheral manifestations of subacute endocarditis (e.g., Janeway lesions; Fig. 31-2A) are related to prolonged infection; with early diagnosis and treatment, these have become infrequent. In contrast, septic embolization mimicking some of these lesions (subungual hemorrhage, Osler’s nodes) is common in patients with acute *S. aureus* endocarditis (Fig. 31-2B). Musculoskeletal pain usually remits promptly with treatment but must be distinguished from focal metastatic infections (e.g., spondylodiscitis), which may complicate 10–15% of cases. Hematogenously seeded focal infection occurs most often in the skin, spleen, kidneys, skeletal system, and meninges. Arterial emboli, one-half of which precede the diagnosis, are clinically apparent in up to 50% of patients. Endocarditis caused by *S. aureus*, vegetations >10 mm in diameter (as measured by echocardiography), and infection involving the mitral valve, especially the anterior leaflet, are independently associated with an increased risk of embolization. Symptoms, pain, or ischemia-induced dysfunction relate to the organ or area suffering embolic arterial occlusion (e.g., kidney, spleen, bowel, extremity). Cerebrovascular emboli presenting as strokes or occasionally as encephalopathy complicate 15–35% of cases of endocarditis. Again, one-half of these events precede the diagnosis of endocarditis. The frequency of stroke is 8 per 1000 patient-days during the week prior to diagnosis; the figure falls to 4.8 and 1.7 per 1000 patient-days during the first and second weeks of effective antimicrobial therapy, respectively. This decline exceeds that which can be attributed to change in vegetation size. Only 3% of strokes occur after 1 week of effective therapy. Emboli occurring late during or after effective therapy do not in themselves constitute evidence of failed antimicrobial treatment.

Other neurologic complications include aseptic or purulent meningitis, intracranial hemorrhage due to hemorrhagic infarcts or ruptured mycotic aneurysms, and seizures. (Mycotic aneurysms are focal dilations of arteries occurring at points in the artery wall that have been weakened by infection in the vasa vasorum or where septic emboli have lodged.) Microabscesses in brain and



A



B

FIGURE 31-2

A. Janeway lesions on toe (left) and plantar surface (right) of the foot in subacute *Neisseria mucosa* endocarditis. (Image courtesy of Rachel Baden, MD.)

B. Septic emboli with hemorrhage and infarction due to acute *Staphylococcus aureus* endocarditis.

meninges occur commonly in *S. aureus* endocarditis; surgically drainable intracerebral abscesses are infrequent.

Immune complex deposition on the glomerular basement membrane causes diffuse hypocomplementemic glomerulonephritis and renal dysfunction, which typically improve with effective antimicrobial therapy. Embolic renal infarcts cause flank pain and hematuria but rarely cause renal dysfunction.

Manifestations of specific predisposing conditions

Almost 50% of endocarditis associated with injection drug use is limited to the tricuspid valve and presents with fever but with faint or no murmur and no peripheral manifestations. Septic pulmonary emboli, which are common with tricuspid endocarditis, cause cough, pleuritic chest pain, nodular pulmonary infiltrates, or occasionally pyopneumothorax. Infection of the aortic or mitral valves presents with the typical clinical features of endocarditis, including peripheral manifestations.

If not associated with a retained intracardiac device or masked by the symptoms of concurrent comorbid illness, health care–associated endocarditis has typical manifestations. CIED endocarditis may be associated with obvious or cryptic generator pocket infection and results in fever, minimal murmur, and pulmonary symptoms due to septic emboli. Late-onset PVE presents with typical clinical features. In cases arising within 60 days of valve surgery (early onset), typical symptoms may be obscured by comorbidity associated with recent surgery. In both early-onset and more delayed presentations, paravalvular infection is common and often results in partial valve dehiscence, regurgitant murmurs, CHF, or disruption of the conduction system.

DIAGNOSIS

In order to avoid delayed or missed diagnosis, careful clinical, microbiologic, and echocardiographic evaluation should be pursued when febrile patients have

348 endocarditis predispositions, cardiac or noncardiac features of endocarditis, or microbiologic findings consistent with endocarditis (e.g., a stroke or splenic infarct, multiple positive blood cultures for an endocarditis-associated organism).

The duke criteria

The diagnosis of infective endocarditis is established with certainty only when vegetations are examined histologically and microbiologically. Nevertheless, a highly sensitive and specific diagnostic schema—known as the modified Duke criteria—is based on clinical, laboratory, and echocardiographic findings commonly encountered in patients with endocarditis (Table 31-3). While developed as a research tool rather than for patient management, the criteria can be a helpful diagnostic

TABLE 31-3
THE MODIFIED DUKE CRITERIA FOR THE CLINICAL DIAGNOSIS OF INFECTIVE ENDOCARDITIS^a

Major Criteria
1. Positive blood culture Typical microorganism for infective endocarditis from two separate blood cultures Viridans streptococci, Streptococcus gallolyticus, HACEK group organisms, Staphylococcus aureus, or Community-acquired enterococci in the absence of a primary focus, or Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from: Blood cultures drawn >12 h apart; or All of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 h apart or Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer of >1:800
2. Evidence of endocardial involvement Positive echocardiogram ^b Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, or Abscess, or New partial dehiscence of prosthetic valve, or New valvular regurgitation (increase or change in preexisting murmur not sufficient)
Minor Criteria
1. Predisposition: predisposing heart conditions ^c or injection drug use

2. Fever ≥38.0°C (≥100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously, ^d or serologic evidence of active infection with an organism consistent with infective endocarditis

^aDefinite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria. See text for further details.
^bTransesophageal echocardiography is required for optimal assessment of possible prosthetic valve endocarditis or complicated endocarditis.
^cValvular disease with stenosis or regurgitation, presence of a prosthetic valve, congenital heart disease including corrected or partially corrected conditions (except isolated atrial septal defect, repaired ventricular septal defect, or closed patent ductus arteriosus), prior endocarditis, or hypertrophic cardiomyopathy.
^dExcluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, or for organisms that do not cause endocarditis frequently, such as gram-negative bacilli.
Source: Adapted from JS Li et al: Clin Infect Dis 30:633, 2000. With permission from Oxford University Press.

tool. If the criteria are to be maximally helpful in evaluating patients, appropriate data must be collected. Furthermore, clinical judgment must be exercised in order to use the criteria effectively. Documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria allows a clinical diagnosis of definite endocarditis. The diagnosis of endocarditis is rejected if an alternative diagnosis is established, if symptoms resolve and do not recur with ≤4 days of antibiotic therapy, or if surgery or autopsy after ≤4 days of antimicrobial therapy yields no histologic evidence of endocarditis. Illnesses not classified as definite endocarditis or rejected as such are considered cases of possible infective endocarditis when either one major and one minor criterion or three minor criteria are fulfilled. Requiring some clinical features of endocarditis for classification as possible infective endocarditis increases the specificity of the schema without significantly reducing its sensitivity. Unless there are extenuating circumstances, patients with definite or possible endocarditis are treated as such.

The criteria emphasize bacteremia and echocardiographic findings typical of endocarditis. The requirement for multiple positive blood cultures over time is consistent with the continuous low-density bacteremia characteristic of endocarditis. Among patients with untreated endocarditis who ultimately have a positive blood culture, 95% of all blood cultures are positive.

The diagnostic criteria attach significance to the species of organism isolated from blood cultures. To fulfill a major criterion, the isolation of an organism that causes both endocarditis and bacteremia in the absence of endocarditis (e.g., *S. aureus*, enterococci) must take place repeatedly (i.e., persistent bacteremia) and in the absence of a primary focus of infection. Organisms that rarely cause endocarditis but commonly contaminate blood cultures (e.g., diphtheroids, CoNS) must be isolated repeatedly if their isolation is to serve as a major criterion.

Blood cultures

Isolation of the causative microorganism from blood cultures is critical for diagnosis and for planning treatment. In patients with suspected NVE, PVE, or CIED endocarditis who have not received antibiotics during the prior 2 weeks, three 2-bottle blood culture sets, separated from one another by at least 2 h, should be obtained from different venipuncture sites over 24 h. If the cultures remain negative after 48–72 h, two or three additional blood culture sets should be obtained, and the laboratory should be consulted for advice regarding optimal culture techniques. Pending culture results, empirical antimicrobial therapy should be withheld initially from hemodynamically stable patients with suspected subacute endocarditis, especially those who have received antibiotics within the preceding 2 weeks. Thus, if necessary, additional blood culture sets can be obtained without the confounding effect of empirical treatment. Patients with acute endocarditis or with deteriorating hemodynamics who may require urgent surgery should receive empirical treatment immediately after three sets of blood cultures are obtained over several hours.

Non-blood-culture tests

Serologic tests can be used to implicate organisms that are difficult to recover by blood culture: *Brucella*, *Bartonella*, *Legionella*, *Chlamydia psittaci*, and *C. burnetii*. Pathogens can also be identified in vegetations by culture, microscopic examination with special stains (i.e., the periodic acid–Schiff stain for *T. whipplei*), or direct fluorescence antibody techniques and by the use of polymerase chain reaction to recover unique microbial DNA or DNA encoding the 16S or 28S ribosomal unit (16S rRNA or 28S rRNA); sequencing of these DNAs allows identification of bacteria and fungi, respectively.

Echocardiography

Echocardiography anatomically confirms and measures vegetations, detects intracardiac complications, and assesses cardiac function (**Fig. 31-3**). Transthoracic

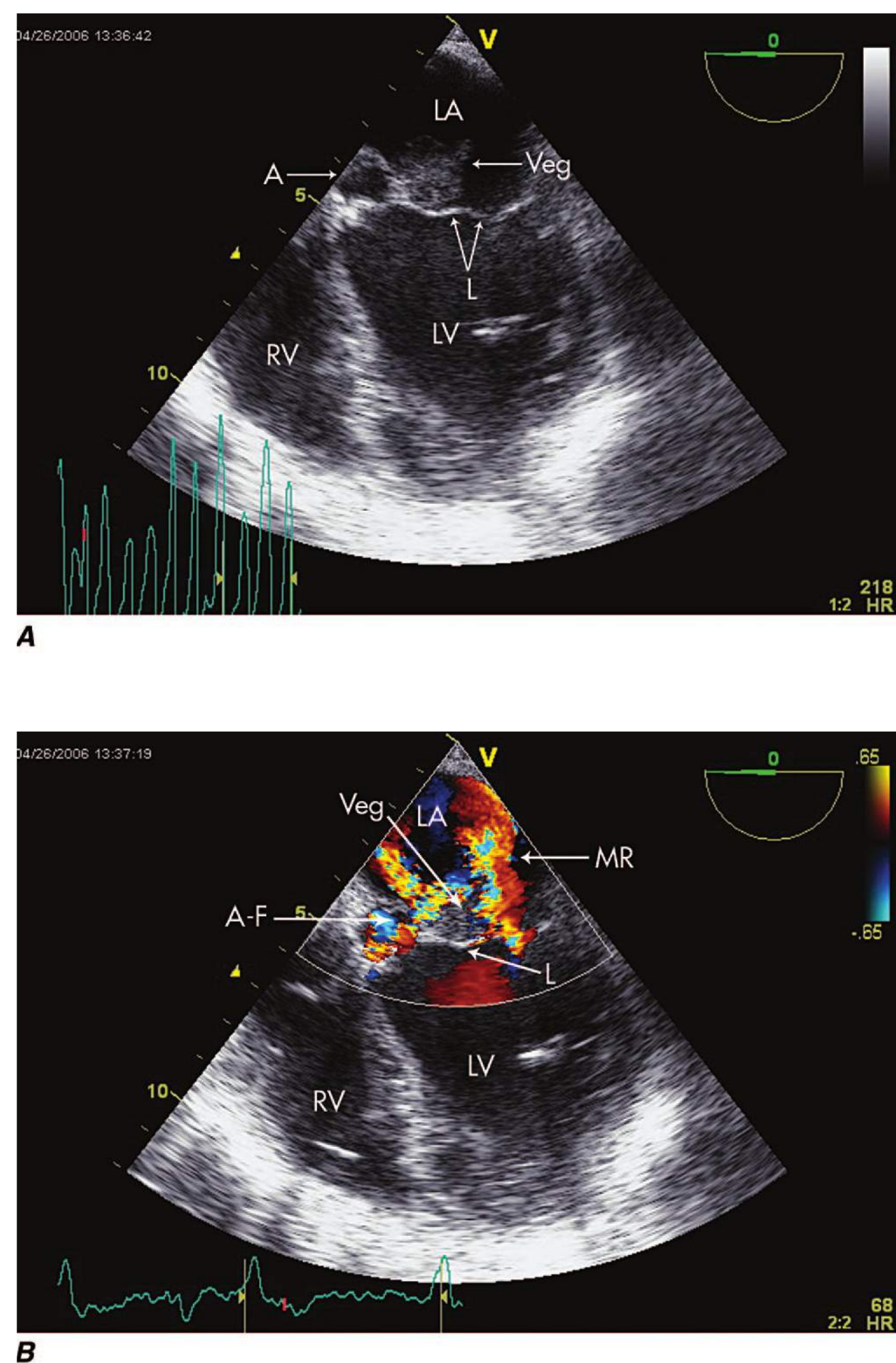


FIGURE 31-3

Imaging of a mitral valve infected with *Staphylococcus aureus* by low-esophageal, four-chamber-view, transesophageal echocardiography (TEE). A Two-dimensional echocardiogram showing a large vegetation with an adjacent echolucent abscess cavity. B Color-flow Doppler image showing severe mitral regurgitation through both the abscess-fistula and the central valve orifice. A, abscess; A-F, abscess-fistula; L, valve leaflets; LA, left atrium; LV, left ventricle; MR, mitral central valve regurgitation; RV, right ventricle; veg, vegetation. (With permission of Andrew Burger, MD.)

echocardiography (TTE) is noninvasive and exceptionally specific; however, it cannot image vegetations <2 mm in diameter, and in 20% of patients it is technically inadequate because of emphysema or body habitus. TTE detects vegetations in 65–80% of patients with definite clinical endocarditis but is not optimal for evaluating prosthetic valves or detecting intracardiac complications. TEE is safe and detects vegetations in >90% of patients with definite endocarditis; nevertheless, initial studies may yield false-negative results in 6–18% of endocarditis patients. When endocarditis is likely, a negative TEE result does not exclude the diagnosis but

350 rather warrants repetition of the study once or twice in 7–10 days. TEE is the optimal method for the diagnosis of PVE, the detection of myocardial abscess, valve perforation, or intracardiac fistulae and for the detection of vegetations in patients with CIED. In patients with CIED and negative blood cultures, a mass adherent to the lead is likely to be a bland thrombosis rather than an infected vegetation.

Because *S. aureus* bacteremia is associated with a high prevalence of endocarditis, routine echocardiographic evaluation (TTE or preferably TEE) is recommended in these patients. Patients with nosocomial *S. aureus* bacteremia are at increased risk of endocarditis if one or more of the following are present: positive blood cultures for 2–4 days, hemodialysis dependency, a permanent intracardiac device, spine infection, non-vertebral osteomyelitis, or an endocarditis-predisposing valve abnormality. Ideally, these patients should be evaluated with TEE. In patients with none of these findings, the risk of endocarditis is low and evaluation with TTE may suffice.

Experts favor echocardiographic evaluation of all patients with a clinical diagnosis of endocarditis; however, the test should not be used to screen patients with a low probability of endocarditis (e.g., patients with unexplained fever). An American Heart Association approach to the use of echocardiography for evaluation of patients with suspected endocarditis is illustrated in (Fig. 31-4).

Other studies

Many studies that are not diagnostic—i.e., complete blood count, creatinine determination, liver function tests, chest radiography, and electrocardiography—are important in the management of patients with endocarditis. The erythrocyte sedimentation rate, C-reactive protein level, and circulating immune complex titer are commonly increased in endocarditis (Table 31-2). Cardiac catheterization is useful primarily to assess coronary artery patency in older individuals who are to undergo surgery for endocarditis.

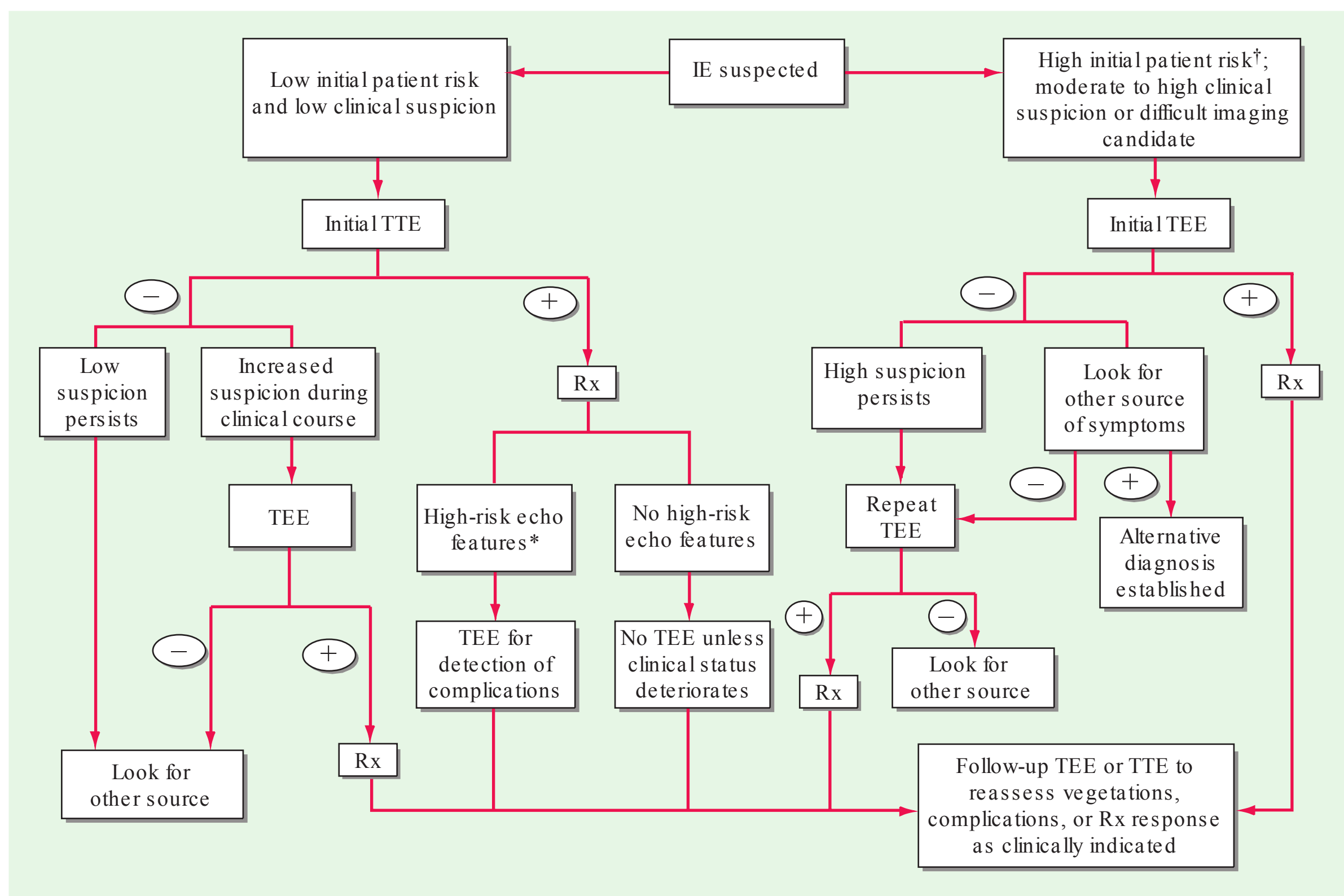


FIGURE 31-4

The diagnostic use of transesophageal and transthoracic echocardiography (TEE and TTE, respectively). †High initial patient risk for infective endocarditis (IE), as listed in Table 31-8, or evidence of intracardiac complications (new regurgitant murmur, new electrocardiographic conduction changes, or congestive heart failure).

*High-risk echocardiographic features include large vegetations, valve insufficiency, paravalvular infection, or ventricular dysfunction. Rx indicates initiation of antibiotic therapy. (Reproduced with permission from Diagnosis and Management of Infective Endocarditis and Its Complications. Circulation 98:2936, 1998. © 1998 American Heart Association.)

TREATMENT Infective Endocarditis

ANTIMICROBIAL THERAPY To cure endocarditis, all bacteria in the vegetation must be killed. However, it is difficult to eradicate these bacteria because local host defenses are deficient and because the bacteria are largely nongrowing and metabolically inactive and thus are less easily killed by antibiotics. Accordingly, therapy must be bactericidal and prolonged. Antibiotics are generally given parenterally to achieve serum concentrations that, through passive diffusion, result in effective concentrations in the depths of the vegetation. To select effective therapy requires knowledge of the susceptibility of the causative microorganisms. The decision to initiate treatment empirically must balance the need to establish a microbiologic diagnosis against the potential progression of disease or the need for urgent surgery (see “Blood Cultures,” earlier). Simultaneous infection at other sites (such as the meninges), allergies, end-organ dysfunction, interactions with concomitantly administered medications, and risks of adverse events must be considered in the selection of therapy.

Although given for several weeks longer, the regimens recommended for the treatment of PVE (except that caused by staphylococci) are similar to those used to treat NVE (Table 31-4). Recommended doses and durations of therapy should be followed unless alterations are required by end-organ dysfunction or adverse events.

Organism-Specific Therapies

Streptococci Optimal therapy for streptococcal endocarditis is based on the minimal inhibitory concentration (MIC) of penicillin for the causative isolate (Table 31-4). The 2-week penicillin/gentamicin or ceftriaxone/gentamicin regimens should not be used to treat PVE or complicated NVE. Caution should be exercised in considering aminoglycoside-containing regimens for the treatment of patients at increased risk for aminoglycoside toxicity. The regimens recommended for relatively penicillin-resistant streptococci are advocated for treatment of group B, C, or G streptococcal endocarditis. Nutritionally variant organisms (*Granulicatella* or *Abiotrophia* species) and *Gemella* species are treated with the regimens for moderately penicillin-resistant streptococci, as is PVE caused by these organisms or by streptococci with a penicillin MIC of $>0.1 \mu\text{g/mL}$ (Table 31-4).

Enterococci Enterococci are resistant to oxacillin, nafcillin, and the cephalosporins and are only inhibited—not killed—by penicillin, ampicillin, teicoplanin (not available in the United States), and vancomycin. To kill enterococci requires the synergistic interaction of a cell wall-active antibiotic that is effective at achievable serum concentrations (penicillin, ampicillin, vancomycin, or teicoplanin) and an aminoglycoside (gentamicin or streptomycin) to which the isolate does not exhibit high-level resistance. An isolate's resistance to cell wall-active agents or its ability to replicate in the presence of gentamicin at $\geq 500 \mu\text{g/mL}$ or streptomycin at $1000\text{--}2000 \mu\text{g/mL}$ —a phenomenon called high-level aminoglycoside resistance—indicates

that the ineffective antimicrobial agent cannot participate in the interaction to produce killing. High-level resistance to gentamicin predicts that tobramycin, netilmicin, amikacin, and kanamycin also will be ineffective. In fact, even when enterococci are not highly resistant to gentamicin, it is difficult to predict the ability of these other aminoglycosides to participate in synergistic killing; consequently, they should not, in general, be used to treat enterococcal endocarditis. High concentrations of ampicillin plus ceftriaxone or cefotaxime, by expanded binding of penicillin-binding proteins, also kill *E. faecalis* in vitro and in animal models of endocarditis.

Enterococci must be tested for high-level resistance to streptomycin and gentamicin, β -lactamase production, and susceptibility to penicillin and ampicillin (MIC, $<8 \mu\text{g/mL}$) and to vancomycin (MIC, $\leq 4 \mu\text{g/mL}$) and teicoplanin (MIC $\leq 2 \mu\text{g/mL}$). If the isolate produces β -lactamase, ampicillin/sulbactam or vancomycin can be used as the cell wall-active component; if the penicillin/ampicillin MIC is $\geq 8 \mu\text{g/mL}$, vancomycin can be considered; and if the vancomycin MIC is $\geq 8 \mu\text{g/mL}$, penicillin or ampicillin can be considered. In the absence of high-level resistance, gentamicin or streptomycin should be used as the aminoglycoside (Table 31-4). Although the dose of gentamicin used to achieve bactericidal synergy in treating enterococcal endocarditis is smaller than that used in standard therapy, nephrotoxicity (or vestibular toxicity with streptomycin) is not uncommon during treatment lasting 4–6 weeks. Regimens in which the aminoglycoside component is given for only 2–3 weeks have been curative and associated with less nephrotoxicity than those using longer courses of gentamicin. Thus regimens wherein gentamicin is administered for only 2–3 weeks are preferred by some.

If there is high-level resistance to both gentamicin and streptomycin, a synergistic bactericidal effect cannot be achieved by the addition of an aminoglycoside; thus no aminoglycoside should be given. Instead, an 8- to 12-week course of a single cell wall-active agent can be considered; for *E. faecalis* endocarditis, high doses of ampicillin combined with ceftriaxone or cefotaxime are suggested (Table 31-4). Non-randomized comparative studies suggest that ampicillin-ceftriaxone may be as effective as (and less nephrotoxic than) penicillin or ampicillin plus an aminoglycoside in the treatment of *E. faecalis* endocarditis. Given the reduced risk of nephrotoxicity with ampicillin-ceftriaxone therapy, this regimen may also be preferred in patients who are at increased risk for aminoglycoside nephrotoxicity.

If the enterococcal isolate is resistant to all of the commonly used agents, suppression of bacteremia followed by surgical treatment should be considered. The role of newer agents potentially active against multidrug-resistant enterococci (quinupristin/dalfopristin [*E. faecium* only], linezolid, and daptomycin) in the treatment of endocarditis has not been established.

Staphylococci The regimens used to treat staphylococcal endocarditis (Table 31-4) are based not on coagulase production but rather on the presence or absence of a prosthetic valve or

TABLE 3 1 -4

ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS ^a		
ORGANISM	DRUG (DOSE, DURATION)	COMMENTS
Streptococci		
Penicillin-susceptible ^b streptococci, <i>S. gallolyticus</i>	• Penicillin G (2–3 mU IVq4h for 4 weeks) • Ceftriaxone (2 g/d IVas a single dose for 4 weeks) • Vancomycin^c (15 mg/kg IVq12h for 4 weeks) • Penicillin G (2–3 mU IVq4h) or ceftriaxone (2 g IV qd) for 2 weeks plus Gentamicin^d (3 mg/kg qd IVor IM, as a single dose^e or divided into equal doses q8h for 2 weeks)	— Can use ceftriaxone in patients with nonimmediate penicillin allergy. Use vancomycin in patients with severe or immediate β-lactam allergy. Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic valve or complicated endocarditis.
Relatively penicillin-resistant ^f	• Penicillin G (4 mU IVq4h) or ceftriaxone (2 g IVqd) for 4 weeks plus Gentamicin^d (3 mg/kg qd IVor IM, as a single dose^e or divided into equal doses q8h for 2 weeks) • Vancomycin^c as noted above for 4 weeks	Penicillin alone at this dose for 6 weeks or with gentamicin during the initial 2 weeks is preferred for prosthetic valve endocarditis caused by streptococci with penicillin MICs of ≤0.1 μg/mL —
Moderately penicillin-resistant ^g streptococci, nutritionally variant organisms, or <i>Gemella</i> species	• Penicillin G (4–5 mU IVq4h) or ceftriaxone (2 g IV qd) for 6 weeks plus Gentamicin^d (3 mg/kg qd IVor IMas a single dose^e or divided into equal doses q8h for 6 weeks) • Vancomycin^c as noted above for 4 weeks	Preferred for prosthetic valve endocarditis caused by streptococci with penicillin MICs of >0.1 μg/mL Regimen is preferred by some.
Enterococci ^h		
	• Penicillin G (4–5 mU IVq4h) plus gentamicin^d (1 mg/kg IVq8h), both for 4–6 weeks • Ampicillin (2 g IVq4h) plus gentamicin^d (1 mg/kg IVq8h), both for 4–6 weeks • Vancomycin^c (15 mg/kg IVq12h) plus gentamicin^d (1 mg/kg IVq8h), both for 4–6 weeks • Ampicillin (2 g IVq4h) plus ceftriaxone (2 g IV q12h), both for 6 weeks	Can use streptomycin (7.5 mg/kg q12h) in lieu of gentamicin if there is not high-level resistance to streptomycin. — Use vancomycin plus gentamicin for penicillin-allergic patients (or desensitize to penicillin) and for isolates resistant to penicillin/ampicillin. Use for <i>E. faecalis</i> isolates with high-level resistance to gentamicin and streptomycin or for patients at high risk for aminoglycoside nephrotoxicity (see text).
Staphylococci		
MSSA infecting native valves (no foreign devices)	• Nafcillin, oxacillin, or flucloxacillin (2 g IVq4h for 4–6 weeks) • Cefazolin (2 g IVq8h for 4–6 weeks) • Vancomycin^c (15 mg/kg IVq12h for 4–6 weeks)	Can use penicillin (4 mU q4h) if isolate is penicillin-susceptible (does not produce β-lactamase). Can use cefazolin regimen for patients with nonimmediate penicillin allergy. Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy; see text regarding addition of gentamicin, fusidic acid, or rifampin.
MRSA infecting native valves (no foreign devices)	• Vancomycin^c (15 mg/kg IVq8–12h for 4–6 weeks)	No role for routine use of rifampin (see text). Consider alternative treatment (see text) for MRSA with vancomycin MIC >1.0 or persistent bacteremia during vancomycin therapy.

TABLE 3 1 -4

ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS ^a		
ORGANISM	DRUG (DOSE, DURATION)	COMMENTS
MSSA infecting prosthetic valves	• Nafcillin, oxacillin, or flucloxacillin (2 g IVq4h for 6–8 weeks) plus Gentamicin ^d (1 mg/kg IM or IVq8h for 2 weeks) plus • Rifampin ⁱ (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine susceptibility to gentamicin before initiating rifampin (see text); if patient is highly allergic to penicillin, use regimen for MRSA; if β-lactam allergy is of the minor nonimmediate type, cefazolin can be substituted for oxacillin/nafcillin.
MRSA infecting prosthetic valves	• Vancomycin ^c (15 mg/kg IVq12h for 6–8 weeks) plus Gentamicin ^d (1 mg/kg IM or IVq8h for 2 weeks) plus Rifampin ⁱ (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility before initiating rifampin (see text).
HACEK Organisms		
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use another third-generation cephalosporin at comparable dosage.
	• Ampicillin/sulbactam (3 g IVq6h for 4 weeks)	—
<i>Coxiella burnetii</i>		
	• Doxycycline (100 mg PO q12h) plus hydroxychloroquine (200 mg PO q8h), both for 18 (native valve) or 24 (prosthetic valve) months	Follow serology to monitor response during treatment (antiphase I IgG and IgA decreased 4-fold and IgM antiphase II negative) and thereafter for relapse.
Bartonella spp.		
	• Ceftriaxone (2 g IVq24h) or ampicillin (2 g IVq4h) or doxycycline (100 mg q12h PO) for 6 weeks plus Gentamicin (1 mg/kg IVq8h for 3 weeks)	If patient is highly allergic to β-lactams, use doxycycline.

^aDoses are for adults with normal renal function. Doses of gentamicin, streptomycin, and vancomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and streptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet). ^bMIC, ≤0.1 μg/mL. ^cVancomycin dose is based on actual body weight. Adjust for trough level of 10–15 μg/mL for streptococcal and enterococcal infections and 15–20 μg/mL for staphylococcal infections. ^dAminoglycosides should not be administered as single daily doses for enterococcal endocarditis and should be introduced as part of the initial treatment. Target peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are ~3.5 μg/mL and ≤1 μg/mL, respectively; target peak and trough serum concentrations of streptomycin (timing as with gentamicin) are 20–35 μg/mL and <10 μg/mL, respectively. ^eNetilmicin (4 mg/kg qd, as a single dose) can be used in lieu of gentamicin. ^fMIC, >0.1 μg/mL and <0.5 μg/mL. ^gMIC, ≥0.5 μg/mL and <8 μg/mL. ^hAntimicrobial susceptibility must be evaluated; see text. ⁱRifampin increases warfarin and dicumarol requirements for anticoagulation. Abbreviations: MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

foreign device, the native valve(s) involved, and the susceptibility of the isolate to penicillin, methicillin, and vancomycin. All staphylococci are considered penicillin-resistant until shown not to produce penicillinase. Similarly, methicillin resistance has become so prevalent among staphylococci that empirical therapy should be initiated with a regimen that covers methicillin-resistant organisms and should later be revised if the isolate proves to be susceptible to methicillin. The addition of 3–5 days of gentamicin to a β-lactam antibiotic or vancomycin to enhance therapy for native mitral or aortic valve endocarditis has not improved survival rates and may be associated with nephrotoxicity. Neither this addition nor the addition of fusidic acid or rifampin is recommended.

For treatment of endocarditis caused by methicillin-resistant *S. aureus* (MRSA), vancomycin, dosed to achieve trough concentrations of 15–20 μg/mL, is recommended,

with the caveat that this regimen may be associated with nephrotoxicity. Although resistance to vancomycin among staphylococci is rare, reduced vancomycin susceptibility among MRSA strains is increasingly encountered. Isolates with a vancomycin MIC of 4–16 μg/mL have intermediate susceptibility and are referred to as vancomycin-intermediate *S. aureus* (VISA). Isolates with an MIC of 2 μg/mL may harbor subpopulations with higher MICs. These heteroresistant VISA (hVISA) isolates are not detectable by routine susceptibility testing. Because of the pharmacokinetics/pharmacodynamics of vancomycin, killing of MRSA with a vancomycin MIC of >1.0 μg/mL is unpredictable, even with aggressive vancomycin dosing. Although not approved by the U.S. Food and Drug Administration for this indication, daptomycin (6 mg/kg [or, as some experts prefer, 8–10 mg/kg] IV once daily) has been recommended as an alternative

to vancomycin, particularly for left-sided endocarditis caused by VISA, hVISA, or isolates with a vancomycin MIC of >1.0 $\mu\text{g/mL}$. These isolates should be tested to document daptomycin susceptibility. Daptomycin activity against MRSA—even against some isolates with reduced daptomycin susceptibility—is enhanced by the addition of nafcillin or ceftaroline. Case reports suggest that either the latter combinations or ceftaroline alone (600 mg IV q8h) may be effective in recalcitrant MRSA endocarditis. Nevertheless, a discussion of treatment of endocarditis in which MRSA bacteremia persists despite therapy is beyond the scope of this chapter and requires consultation with an infectious disease specialist. The efficacy of linezolid for left-sided MRSA endocarditis has not been established. Although not widely adopted by other groups, the recommendation of the British Society for Antimicrobial Chemotherapy is that a second drug be added to vancomycin (rifampin) or to daptomycin (rifampin, gentamicin, or linezolid) for the treatment of NVE due to MRSA.

Methicillin-susceptible *S. aureus* endocarditis that is uncomplicated and limited to the tricuspid or pulmonic valve can often be treated with a 2-week course that combines oxacillin or nafcillin (but not vancomycin) with gentamicin. However, patients with prolonged fever (≥ 5 days) during therapy or multiple septic pulmonary emboli should receive standard-duration therapy. Vancomycin plus gentamicin for 2 weeks as treatment for right-sided endocarditis caused by MRSA yields suboptimal results; thus this entity is treated for 4 weeks with vancomycin or daptomycin (6 mg/kg as a single daily dose).

Staphylococcal PVE is treated for 6–8 weeks with a multidrug regimen. Rifampin is an essential component because it kills staphylococci that are adherent to foreign material in a biofilm. Two other agents (selected on the basis of susceptibility testing) are combined with rifampin to prevent in vivo emergence of resistance. Because many staphylococci (particularly MRSA and *Staphylococcus epidermidis*) are resistant to gentamicin, the isolate's susceptibility to gentamicin or an alternative agent should be established before rifampin treatment is begun. If the isolate is resistant to gentamicin, then another aminoglycoside, a fluoroquinolone (chosen on the basis of susceptibility), or another active agent should be substituted for gentamicin.

Other Organisms In the absence of meningitis, endocarditis caused by *Streptococcus pneumoniae* isolates with a penicillin MIC of ≤ 1 $\mu\text{g/mL}$ can be treated with IV penicillin (4 million units every 4 h), ceftriaxone (2 g/d as a single dose), or cefotaxime (at a comparable dosage). Infection caused by pneumococcal strains with a penicillin MIC of ≥ 2 $\mu\text{g/mL}$ should be treated with vancomycin. If meningitis is suspected or present, treatment with vancomycin plus ceftriaxone—at the doses advised for meningitis—should be initiated until susceptibility results are known. Definitive therapy should then be selected on the basis of meningitis breakpoints (penicillin MIC, 0.06 $\mu\text{g/mL}$; or ceftriaxone MIC, 0.5 $\mu\text{g/mL}$). *P. aeruginosa* endocarditis is treated with an antipseudomonal penicillin (ticarcillin or

piperacillin) and high doses of tobramycin (8 mg/kg per day in three divided doses). Endocarditis caused by Enterobacteriaceae is treated with a potent β -lactam antibiotic plus an aminoglycoside. Corynebacterial endocarditis is treated with a penicillin plus an aminoglycoside (if the organism is susceptible to the aminoglycoside) or with vancomycin, which is highly bactericidal for most strains. Therapy for *Candida* endocarditis consists of amphotericin B plus flucytosine and early surgery; long-term (if not indefinite) suppression with an oral azole is advised. Echinocandin treatment of *Candida* endocarditis has been effective in sporadic cases; nevertheless, the role of echinocandins in this setting has not been established.

Empirical therapy In designing therapy (largely with antimicrobials and doses from Table 31-4 to target putative microorganisms) to be administered before culture results are known or when cultures are negative, clinical clues (e.g., acute vs. subacute presentation, site of infection, patient's predispositions) as well as epidemiologic clues to etiology must be considered. Thus empirical therapy for acute endocarditis in an injection drug user should cover MRSA and gram-negative bacilli. Treatment with vancomycin plus gentamicin, initiated immediately after blood samples are obtained for culture, covers these organisms as well as many other potential causes. Similarly, treatment of health care–associated endocarditis must cover MRSA. In the treatment of culture-negative episodes, marantic endocarditis must be excluded and fastidious organisms sought by serologic testing. In the absence of prior antibiotic therapy, it is unlikely that *S. aureus*, CoNS, or enterococcal infection will present with negative blood cultures; thus, in this situation, recommended empirical therapy targets not these organisms but rather nutritionally variant organisms, the HACEK group, and *Bartonella* species. Pending the availability of diagnostic data, blood culture–negative subacute NVE is treated with gentamicin plus ampicillin-sulbactam (12 g every 24 h) or ceftriaxone; doxycycline (100 mg twice daily) is added for enhanced *Bartonella* coverage. For culture-negative PVE, vancomycin, gentamicin, cefepime, and rifampin should be used if the prosthetic valve has been in place for ≤ 1 year. Empirical therapy for infected prosthetic valves in place for >1 year is similar to that for culture-negative NVE. If cultures may be negative because of confounding by prior antibiotic administration, broader empirical therapy may be indicated, with particular attention to pathogens that are likely to be inhibited by the specific prior therapy.

CIED Endocarditis Antimicrobial therapy for CIED endocarditis is adjunctive to complete device removal. The antimicrobial selected is based on the causative organism and should be used as recommended for NVE (Table 31-4). Bacteremic CIED infection may be complicated by coincident NVE or remote-site infection (e.g., osteomyelitis). A 4- to 6-week course of endocarditis-targeted therapy is recommended for patients with CIED endocarditis and for those with bacteremia that continues during ongoing antimicrobial therapy after device removal. Although *S. aureus* bacteremia (and persistent CoNS

bacteremia) in patients who have a CIED in place is likely—in the absence of another source—to reflect endocarditis and should be managed accordingly, not all bloodstream infections in these patients indicate endocarditis. If evidence suggesting endocarditis is lacking, bloodstream infection due to gram-negative bacilli, streptococci, enterococci, and *Candida* species may not indicate device infection. However, in the absence of another source, relapse after antimicrobial therapy increases the likelihood of CIED endocarditis and warrants treatment as such.

Outpatient Antimicrobial Therapy

Fully compliant, clinically stable patients who are no longer bacteremic, are not febrile, and have no clinical or echocardiographic findings that suggest an impending complication may complete therapy as outpatients. Careful follow-up and a stable home setting are necessary, as are predictable IV access and use of antimicrobial agents that are stable in solution. Recommended regimens should not be compromised to accommodate outpatient therapy.

Monitoring Antimicrobial Therapy Measurement of the serum bactericidal titer—the highest dilution of the patient’s serum during therapy that kills 99.9% of the standard inoculum of the infecting organism—is not recommended for assessment of standard regimens but may be useful for assessment of the treatment of endocarditis caused by unusual organisms. Serum concentrations of aminoglycosides and vancomycin should be monitored and doses adjusted to avoid or address toxicity.

Antibiotic toxicities, including allergic reactions, occur in 25–40% of patients and commonly arise after several weeks of therapy. Blood tests to detect renal, hepatic, and hematologic toxicity should be performed periodically.

Blood cultures should be repeated daily until sterile in patients with endocarditis due to *S. aureus* or difficult-to-treat organisms, rechecked if there is recrudescence fever, and performed again 4–6 weeks after therapy to document cure. Blood cultures become sterile within 2 days after the start of appropriate therapy when infection is caused by viridans streptococci, enterococci, or HACEK organisms. In *S. aureus* endocarditis, β -lactam therapy results in sterile cultures in 3–5 days, whereas in MRSA endocarditis, positive cultures may persist for 7–9 days with vancomycin or daptomycin treatment. MRSA bacteremia persisting despite an adequate dosage of vancomycin may indicate infection due to a strain with reduced vancomycin susceptibility and therefore may point to a need for alternative therapy. When fever persists for 7 days despite appropriate antibiotic therapy, patients should be evaluated for paravalvular abscess, extracardiac abscesses (spleen, kidney), or complications (embolic events). Recrudescence fever raises the possibility of these complications but also of drug reactions or complications of hospitalization. Vegetations become smaller with effective therapy; however, 3 months after cure, 50% are unchanged and 25% are slightly larger.

SURGICAL TREATMENT Intracardiac and central nervous system complications are important causes of morbidity and death due to infective endocarditis. In some cases, effective treatment for these complications requires surgery. The indications for cardiac surgical treatment of endocarditis (Table 31-5) have been derived from observational studies and expert opinion. The strength of individual indications varies; thus the risks and benefits as well as the timing of surgery must be individualized (Table 31-6). From 25% to 40% of patients with left-sided endocarditis undergo cardiac surgery during active infection, with slightly higher surgery rates for PVE than NVE. Intracardiac complications (which are most reliably detected by TEE) and CHF are the most commonly cited indications for surgery. The benefit of surgery has been assessed primarily in studies comparing populations of medically and surgically treated patients matched for the necessity of surgery (indications assessed in studies as propensity), with adjustments for predictors of death (comorbidities) and timing of the surgical intervention. Although study results vary, surgery for currently advised indications appears to convey a significant survival benefit (27–55%) that becomes apparent only with follow-up for ≥ 6 months. During the initial weeks after surgery, mortality risk may appear increased (disease + surgery-related mortality).

TABLE 31-5

INDICATIONS FOR CARDIAC SURGICAL INTERVENTION IN PATIENTS WITH ENDOCARDITIS	
Surgery Required for Optimal Outcome	
Moderate to severe congestive heart failure due to valve dysfunction	
Partially dehiscence unstable prosthetic valve	
Persistent bacteremia despite optimal antimicrobial therapy	
Lack of effective microbicidal therapy (e.g., fungal or <i>Brucella</i> endocarditis)	
<i>S. aureus</i> prosthetic valve endocarditis with an intracardiac complication	
Relapse of prosthetic valve endocarditis after optimal antimicrobial therapy	
Surgery to Be Strongly Considered for Improved Outcome ^a	
Perivalvular extension of infection	
Poorly responsive <i>S. aureus</i> endocarditis involving the aortic or mitral valve	
Large (>10 mm in diameter) hypermobile vegetations with increased risk of embolism, particularly with prior embolic event or with significant valve dysfunction	
Persistent unexplained fever (≥ 10 days) in culture-negative native valve endocarditis	
Poorly responsive or relapsed endocarditis due to highly antibiotic-resistant enterococci or gram-negative bacilli	

^aSurgery must be carefully considered; findings are often combined with other indications to prompt surgery.

TABLE 3 1 -6
TIMING OF CARDIAC SURGICAL INTERVENTION IN PATIENTS WITH ENDOCARDITIS

INDICATION FOR SURGICAL INTERVENTION		
TIMING	STRONG SUPPORTING EVIDENCE	CONFLICTING EVIDENCE, BUT MAJORITY OF OPINIONS FAVOR SURGERY
Emergent (same day)	Acute aortic regurgitation plus preclosure of mitral valve	
	Sinus of Valsalva abscess ruptured into right heart	
	Rupture into pericardial sac	
Urgent (within 1–2 days)	Valve obstruction by vegetation	Major embolus plus persisting large vegetation (>10 mm in diameter)
	Unstable (dehiscenced) prosthesis	
	Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV)	
	Septal perforation	
Elective (earlier usually preferred)	Perivalvular extension of infection with or without new electrocardiographic conduction system changes	
	Lack of effective antibiotic therapy	
	Vegetation diameter >10 mm plus severe aortic or mitral valve dysfunction ^a	Staphylococcal prosthetic valve endocarditis
	Progressive paravalvular prosthetic regurgitation	Early prosthetic valve endocarditis (≤2 months after valve surgery)
	Valve dysfunction plus persisting infection after ≥7–10 days of antimicrobial therapy	Fungal endocarditis (<i>Candida</i> spp.)
	Fungal (mold) endocarditis	Antibiotic-resistant organisms

^aSupported by a single-institution randomized trial showing benefit from early surgery. Implementation requires clinical judgment.
Source: Adapted from LOlaison, G Pettersson: Infect Dis Clin North Am 16:453, 2002.

Indications

Congestive Heart Failure Moderate to severe refractory CHF caused by new or worsening valve dysfunction is the major indication for cardiac surgery. At 6 months of follow-up, patients with left-sided endocarditis and moderate to severe heart failure due to valve dysfunction who are treated medically have a 50% mortality rate, while among matched patients who undergo surgery the mortality rate is 15%. The survival benefit with surgery, which is most predictable among patients with the most weighty indications (propensity), is seen in both NVE and PVE. Surgery can relieve functional stenosis due to large vegetations or restore competence to damaged regurgitant valves by repair or replacement.

Perivalvular Infection This complication, which is most common with aortic valve infection, occurs in 10–15% of native valve and 45–60% of prosthetic valve infections. It is suggested by persistent unexplained fever during appropriate therapy, new electrocardiographic conduction disturbances, or pericarditis. TEE with color Doppler is the test of choice to detect perivalvular abscesses (sensitivity, ≥85%). For optimal outcome, surgery is required, especially when fever persists, fistulae develop, prostheses are dehiscenced and unstable, or infection relapses after appropriate treatment. Cardiac rhythm must be monitored since high-grade heart block may require insertion of a pacemaker.

Uncontrolled Infection Continued positive blood cultures or otherwise-unexplained persistent fevers (in patients with either blood culture–positive or –negative endocarditis) despite

optimal antibiotic therapy may reflect uncontrolled infection and may warrant surgery. Surgical treatment is also advised for endocarditis caused by organisms against which effective antimicrobial therapy is lacking (e.g., yeasts, fungi, *P. aeruginosa*, other highly resistant gram-negative bacilli, *Brucella* species).

S. Aureus Endocarditis The mortality rate for *S. aureus* PVE exceeds 50% with medical treatment but is reduced to 25% with surgical treatment. In patients with intracardiac complications associated with *S. aureus* PVE, surgical treatment reduces the mortality rate twentyfold. Surgical treatment should be considered for patients with *S. aureus* native aortic or mitral valve infection who have TTE-demonstrable vegetations and remain septic during the initial week of therapy. Isolated tricuspid valve endocarditis, even with persistent fever, rarely requires surgery.

Prevention of Systemic Emboli Death and persisting morbidity may result from cerebral or coronary artery emboli. Predicting a high risk of systemic embolization by echocardiographic determination of vegetation size and anatomy does not by itself identify those patients in whom surgery to prevent emboli will result in increased chances of survival. Net benefits from surgery to prevent emboli are most likely when other surgical benefits can be achieved simultaneously—e.g., repair of a moderately dysfunctional valve or debridement of a paravalvular abscess. Only 3.5% of patients undergo surgery solely to prevent systemic emboli. Valve repair, with the consequent avoidance of prosthesis insertion, improves the benefit-to-risk ratio of surgery performed to address vegetations.

Infected Endocarditis Removal of all hardware is recommended for patients with established CIED infection (pocket or intracardiac lead) or erosion of the device through the skin. Percutaneous lead extraction is preferred. With lead vegetations of >3 cm and the resulting risk of a pulmonary embolus or with retained hardware after attempted percutaneous extraction, surgical removal should be considered. Removal of the infected CIED during the initial hospitalization is associated with increased 30-day and 1-year survival rates over those attained with antibiotic therapy and device retention. If necessary, the CIED can be reimplemented percutaneously or surgically (epicardial leads) at a new site after at least 10–14 days of effective antimicrobial therapy. CIEDs should be removed and replaced subsequently when patients undergo valve surgery for endocarditis.

Timing Of Cardiac Surgery With the more life-threatening indications for surgery (valve dysfunction and severe CHF, paravalvular abscess, major prosthesis dehiscence), early surgery—i.e., during the initial week of therapy—is associated with a greater chance of survival than later surgery. With less compelling indications, surgery may reasonably be delayed to allow further treatment as well as improvement in overall health (Table 31-6). After 14 days of recommended antibiotic therapy, excised valves are culture-negative in 99% and 50% of patients with streptococcal and *S. aureus* endocarditis, respectively. Recrudescence of endocarditis on a new implanted prosthetic valve follows surgery for active NVE and PVE in 2% and 6–15% of patients, respectively. These frequencies do not justify the risk of an adverse outcome due to a delay in surgery, particularly in patients with severe heart failure, valve dysfunction, and uncontrolled staphylococcal infections. Delay is justified when infection is controlled and CHF is resolved with medical therapy.

Neurologic complications of endocarditis may be exacerbated as a consequence of cardiac surgery. The risk of neurologic deterioration is related to the type of neurologic complication and the interval between the complication and surgery. Whenever feasible, cardiac surgery should be delayed for 2–3 weeks after a nonhemorrhagic embolic infarction and for 4 weeks after a cerebral hemorrhage. A ruptured mycotic aneurysm should be treated before cardiac surgery. **Antibiotic Therapy after Cardiac Surgery**

Organisms have been detected on Gram's stain—or their DNA has been detected by polymerase chain reaction—in excised valves from 45% of patients who have successfully completed the recommended therapy for endocarditis. In only 7% of these patients are the organisms, most of which are unusual and antibiotic resistant, cultured from the valve. Detection of organisms or their DNA does not necessarily indicate antibiotic failure; in fact, relapse of endocarditis after surgery is uncommon. Thus, when valve cultures are negative in uncomplicated NVE caused by susceptible organisms, the duration of preoperative plus postoperative treatment should equal the total duration of recommended therapy, with ~2 weeks of treatment administered after surgery. For

endocarditis complicated by paravalvular abscess, partially treated PVE, or cases with culture-positive valves, a full course of therapy should be given postoperatively.

Extracardiac Complications Splenic abscess develops in 3–5% of patients with endocarditis. Effective therapy requires either image-guided percutaneous drainage or splenectomy. Mycotic aneurysms occur in 2–15% of endocarditis patients; one-half of these cases involve the cerebral arteries and present as headaches, focal neurologic symptoms, or hemorrhage. Cerebral aneurysms should be monitored by angiography. Some will resolve with effective antimicrobial therapy, but those that persist, enlarge, or leak should be treated surgically if possible. Extracerebral aneurysms present as local pain, a mass, local ischemia, or bleeding; these aneurysms are treated surgically.

OUTCOME

Factors that can adversely affect outcome include older age, severe comorbid conditions and diabetes, delayed diagnosis, involvement of prosthetic valves or the aortic valve, an invasive (*S. aureus*) or antibiotic-resistant (*P. aeruginosa*, yeast) pathogen, intracardiac and major neurologic complications, and an association with health care. Death and poor outcome often are related not to failure of antibiotic therapy but rather to the interactions of comorbidities and endocarditis-related end-organ complications. In developed countries, overall survival rates are 80–85%; however, rates vary considerably among subpopulations of endocarditis patients. Survival rates for patients with NVE caused by viridans streptococci, HACEK organisms, or enterococci (susceptible to synergistic therapy) are 85–90%. For *S. aureus* NVE in patients who do not inject drugs, survival rates are 55–70%, whereas 85–90% of injection drug users survive this infection. PVE beginning within 2 months of valve replacement results in mortality rates of 40–50%, whereas rates are only 10–20% in later-onset cases.

PREVENTION

To prevent endocarditis (long a goal in clinical practice), past expert committees have supported systemic antibiotic administration prior to many bacteremia-inducing procedures. A reappraisal of the evidence for antibiotic prophylaxis for endocarditis by the American Heart Association and the European Society of Cardiology culminated in guidelines advising its more restrictive use. At best, the benefit of antibiotic prophylaxis is minimal. Most endocarditis cases do not follow a procedure. Although dental treatments have been widely considered to predispose to endocarditis, such infection occurs no more frequently in patients who are undergoing dental treatment than in matched controls who are

358 not. Furthermore, the frequency and magnitude of bacteremia associated with dental procedures and a routine day's activities (e.g., tooth brushing and flossing) are similar; because dental procedures are infrequent events, exposure of cardiac structures to bacteremic oral-cavity organisms is notably greater from routine daily activities than from dental care. The relation of gastrointestinal and genitourinary procedures to subsequent endocarditis is even more tenuous than that of dental procedures. In addition, cost-effectiveness and cost-benefit estimates suggest that antibiotic prophylaxis represents a poor use of resources.

Nevertheless, studies in animal models suggest that antibiotic prophylaxis may be effective. Thus it is possible that rare cases of endocarditis are prevented. Weighing the potential benefits, potential adverse events, and costs associated with antibiotic prophylaxis, the American Heart Association and the European Society of Cardiology now recommend prophylactic antibiotics (Table 31-7) only for those patients at highest

TABLE 31-7
ANTIBIOTIC REGIMENS FOR PROPHYLAXIS OF ENDOCARDITIS IN ADULTS WITH HIGH-RISK CARDIAC LESIONS^{a,b}

A. Standard oral regimen
Amoxicillin: 2 g PO 1 h before procedure
B. Inability to take oral medication
Ampicillin: 2 g IV or IM within 1 h before procedure
C. Penicillin allergy
1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure
2. Cephalexin ^c : 2 g PO 1 h before procedure
3. Clindamycin: 600 mg PO 1 h before procedure
D. Penicillin allergy, inability to take oral medication
1. Cefazolin ^c or ceftriaxone ^c : 1 g IV or IM 30 min before procedure
2. Clindamycin: 600 mg IV or IM 1 h before procedure

^aDosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV. ^bFor high-risk lesions, see Table 31-8. Prophylaxis is not advised for other lesions. ^cDo not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin. Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: Circulation 116:1736, 2007; and G Habib et al: Eur Heart J 30:2369, 2009).

TABLE 31-8

HIGH-RISK CARDIAC LESIONS FOR WHICH ENDOCARDITIS PROPHYLAXIS IS ADVISED BEFORE DENTAL PROCEDURES
Prosthetic heart valves
Prior endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
Completely repaired congenital heart defects during the 6 months after repair
Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material
Valvulopathy developing after cardiac transplantation ^a

^aNot a target population for prophylaxis according to recommendations of the European Society of Cardiology. Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: Circulation 116:1736, 2007; and G Habib et al: Eur Heart J 30:2369, 2009).

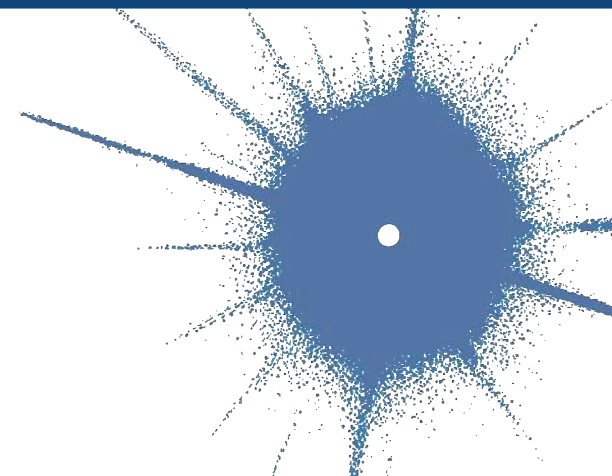
risk for severe morbidity or death from endocarditis (Table 31-8). Maintaining good dental hygiene is essential. Prophylaxis is recommended only when there is manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa (including surgery on the respiratory tract). Prophylaxis is not advised for patients undergoing gastrointestinal or genitourinary tract procedures. High-risk patients should be treated before or when they undergo procedures on an infected genitourinary tract or on infected skin and soft tissue.

In patients with aortic or mitral valve regurgitation or a prosthetic valve, treatment of acute Q fever with doxycycline plus hydroxychloroquine (for doses, see Table 31-4) for 12 months is highly effective in preventing *C. burnetii* endocarditis.

The National Institute for Health and Clinical Excellence in the United Kingdom has advised discontinuation of all antibiotic prophylaxis for endocarditis. Limited surveillance studies have not detected increased viridans streptococcal endocarditis subsequent to the promulgation of guidelines that are more restrictive or advise no prophylaxis.

CHAPTER 32

ACUTE RHEUMATIC FEVER



Jonathan R. Carapetis

Acute rheumatic fever (ARF) is a multisystem disease resulting from an autoimmune reaction to infection with group A streptococcus. Although many parts of the body may be affected, almost all of the manifestations resolve completely. The major exception is cardiac valvular damage (rheumatic heart disease [RHD]), which may persist after the other features have disappeared.

GLOBAL CONSIDERATIONS



ARF and RHD are diseases of poverty. They were common in all countries until the early twentieth century, when their incidence began to decline in industrialized nations. This decline was largely attributable to improved living conditions—particularly less crowded housing and better hygiene—which resulted in reduced transmission of group A streptococci. The introduction of antibiotics and improved systems of medical care had a supplemental effect.

The virtual disappearance of ARF and reduction in the incidence of RHD in industrialized countries during the twentieth century unfortunately was not replicated in developing countries, where these diseases continue unabated. RHD is the most common cause of heart disease in children in developing countries and is a major cause of mortality and morbidity in adults as well. It has been estimated that between 15 and 19 million people worldwide are affected by RHD, with approximately one-quarter of a million deaths occurring each year. Some 95% of ARF cases and RHD deaths now occur in developing countries, with particularly high rates in sub-Saharan Africa, Pacific nations, Australasia, and South and Central Asia. The pathogenic pathway from exposure to group A streptococcus followed by pharyngeal infection and subsequent development of ARF, ARF recurrences, and development of

RHD and its complications is associated with a range of risk factors and, therefore, potential interventions at each point (**Fig. 32-1**). In affluent countries, many of these risk factors are well controlled, and where needed, interventions are in place. Unfortunately, the greatest burden of disease is found in developing countries, most of which do not have the resources, capacity, and/or interest to tackle this multifaceted disease. In particular, almost none of the developing countries has a coordinated, register-based RHD control program, which is proven to be cost effective in reducing the burden of RHD. Enhancing awareness of RHD and mobilizing resources for its control in developing countries are issues requiring international attention.

EPIDEMIOLOGY

ARF is mainly a disease of children age 5–14 years. Initial episodes become less common in older adolescents and young adults and are rare in persons age >30 years. By contrast, recurrent episodes of ARF remain relatively common in adolescents and young adults. This pattern contrasts with the prevalence of RHD, which peaks between 25 and 40 years. There is no clear gender association for ARF, but RHD more commonly affects females, sometimes up to twice as frequently as males.

PATHOGENESIS

ORGANISM FACTORS

Based on currently available evidence, ARF is exclusively caused by infection of the upper respiratory tract with group A streptococci. Although classically, certain M-serotypes (particularly types 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29) were associated with ARF, in high-incidence regions, it is now thought that any strain of

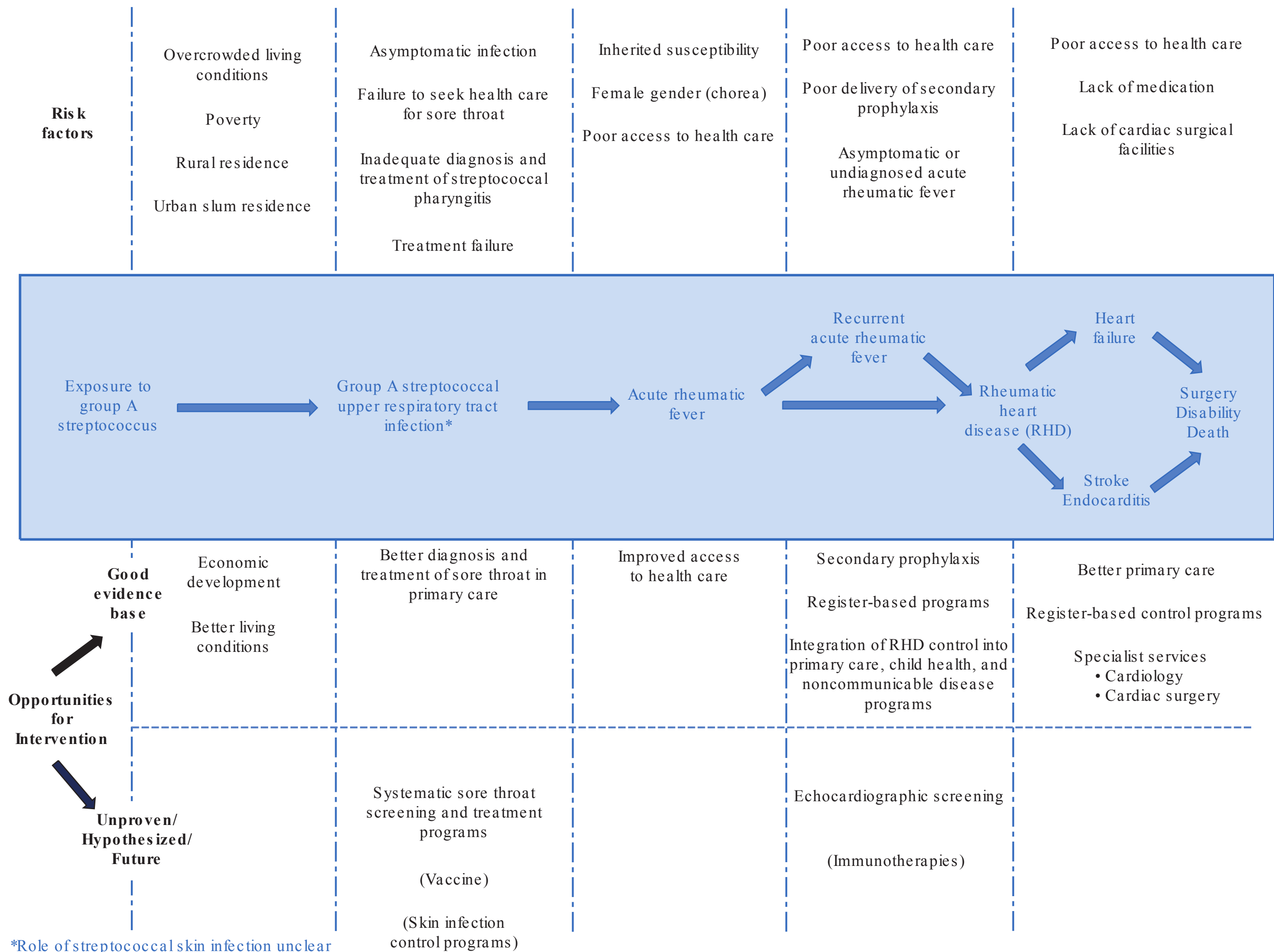


FIGURE 32-1
Pathogenetic pathway for acute rheumatic fever and rheumatic heart disease, with associated risk factors and opportunities for

intervention at each step. Interventions in parentheses are either unproven or currently unavailable.

group A streptococcus has the potential to cause ARF. The potential role of skin infection and of groups C and G streptococci is currently being investigated.

HOST FACTORS

Approximately 3–6% of any population may be susceptible to ARF, and this proportion does not vary dramatically between populations. Findings of familial clustering of cases and concordance in monozygotic twins—particularly for chorea—confirm that susceptibility to ARF is an inherited characteristic, with 44% concordance in monozygotic twins compared to 12% in dizygotic twins, and heritability more recently estimated at 60%. Most evidence for host factors focuses on immunologic determinants. Some human leukocyte antigen (HLA) class II alleles, particularly HLA-DR7 and HLA-DR4, appear to be associated with susceptibility, whereas other class II alleles have been associated with protection (HLA-DR5, HLA-DR6, HLA-DR51, HLA-DR52,

and HLA-DQ). Associations have also been described with polymorphisms at the tumor necrosis factor α locus (TNF- α -308 and TNF- α -238), high levels of circulating mannose-binding lectin, and Toll-like receptors.

THE IMMUNE RESPONSE

The most widely accepted theory of rheumatic fever pathogenesis is based on the concept of molecular mimicry, whereby an immune response targeted at streptococcal antigens (mainly thought to be on the M protein and the N-acetylglucosamine of group A streptococcal carbohydrate) also recognizes human tissues. In this model, cross-reactive antibodies bind to endothelial cells on the heart valve, leading to activation of the adhesion molecule VCAM-1, with resulting recruitment of activated lymphocytes and lysis of endothelial cells in the presence of complement. The latter leads to release of peptides including laminin, keratin, and tropomyosin, which, in turn, activates cross-reactive T cells that

invade the heart, amplifying the damage and causing epitope spreading. An alternative hypothesis proposes that the initial damage is due to streptococcal invasion of epithelial surfaces, with binding of M protein to type IV collagen RHD allowing it to become immunogenic, but not through the mechanism of molecular mimicry.

CLINICAL FEATURES

There is a latent period of ~3 weeks (1–5 weeks) between the precipitating group A streptococcal infection and the appearance of the clinical features of ARF. The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing. The most common clinical features are polyarthritides (present in 60–75% of cases) and carditis (50–60%). The prevalence of chorea in ARF varies substantially between populations, ranging from <2 to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of cases.

HEART INVOLVEMENT

Up to 60% of patients with ARF progress to RHD. The endocardium, pericardium, or myocardium may be affected. Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost always affected, sometimes together with the aortic valve; isolated aortic valve involvement is rare. Damage to the pulmonary or tricuspid valves is usually secondary to increased pulmonary pressures resulting from left-sided valvular disease. Early valvular damage leads to regurgitation. Over ensuing years, usually as a result of recurrent episodes, leaflet thickening, scarring, calcification, and valvular stenosis may develop (Fig. 32-2). See Videos 32-1 and 32-2 via the <https://www.mhprofessional.com/mediacenter/>. Therefore, the characteristic manifestation of carditis in previously unaffected individuals is mitral regurgitation, sometimes accompanied by aortic regurgitation. Myocardial inflammation may affect electrical conduction pathways, leading to P-R interval prolongation (first-degree atrioventricular block or rarely higher level block) and softening of the first heart sound.

People with RHD are often asymptomatic for many years before their valvular disease progresses to cause cardiac failure. Moreover, particularly in resource-poor settings, the diagnosis of ARF is often not made, so children, adolescents, and young adults may have RHD but not know it. These cases can be diagnosed using echocardiography; auscultation is poorly sensitive and specific for RHD diagnosis in asymptomatic patients.

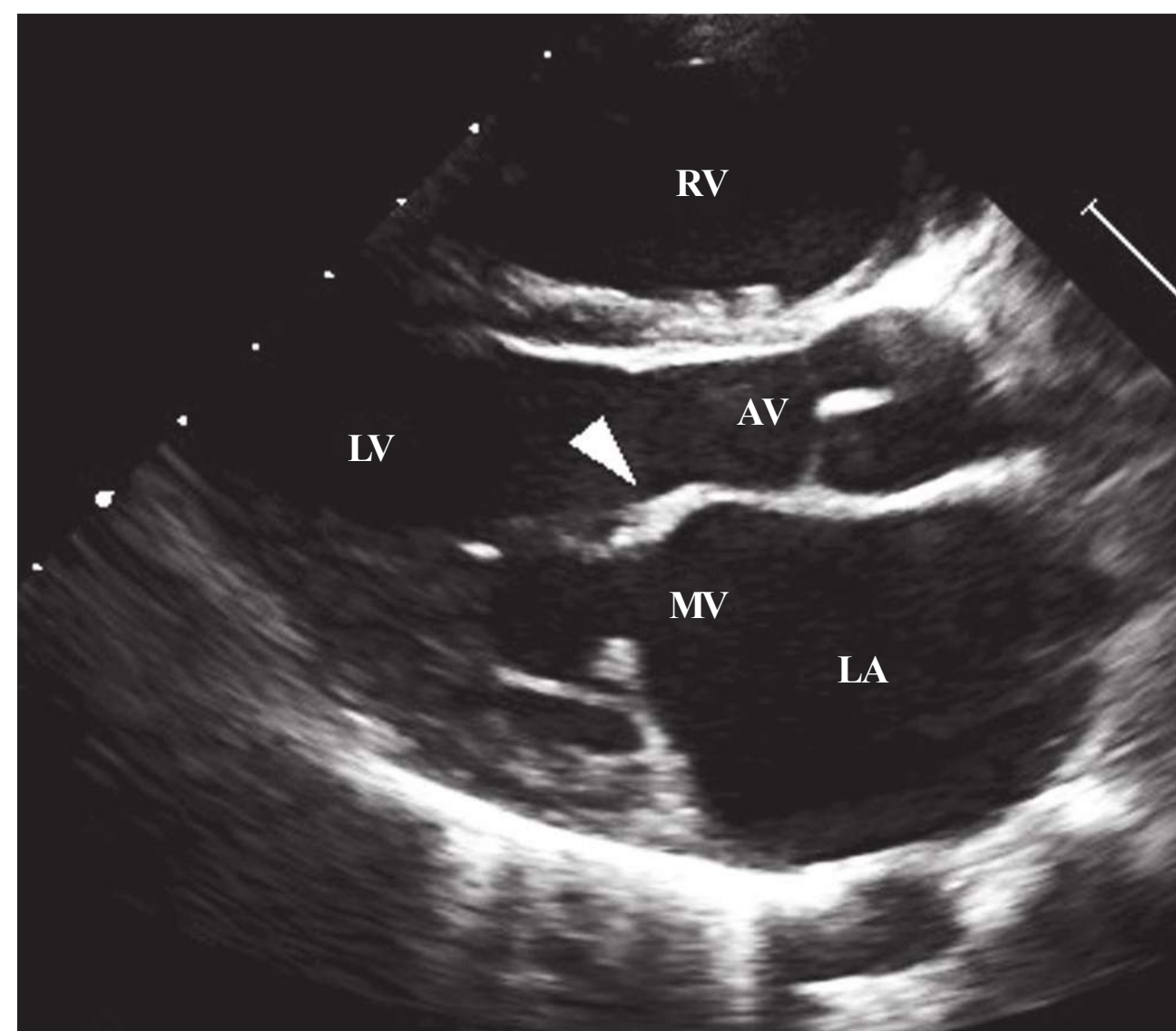


FIGURE 32-2

Transthoracic echocardiographic image from a 5-year-old boy with chronic rheumatic heart disease. This diastolic image demonstrates leaflet thickening, restriction of the anterior mitral valve leaflet tip and doming of the body of the leaflet toward the interventricular septum. This appearance (marked by the arrowhead) is commonly described as a “hockey stick” or an “elbow” deformity. AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. (Courtesy of Dr. Bo Remyenyi, Department of Paediatric and Congenital Cardiac Services, Starship Children’s Hospital, Auckland, New Zealand.)

Echocardiographic screening of school-aged children in populations with high rates of RHD is becoming more widespread and has been facilitated by improving technologies in portable echocardiography and the availability of consensus guidelines for the diagnosis of RHD on echocardiography (Table 32-1). Although a diagnosis of definite RHD on screening echocardiography should lead to commencement of secondary prophylaxis, the clinical significance of borderline RHD has yet to be determined.

JOINT INVOLVEMENT

The most common form of joint involvement in ARF is arthritis, i.e., objective evidence of inflammation, with hot, swollen, red, and/or tender joints, and involvement of more than one joint (i.e., polyarthritides). Polyarthritides is typically migratory, moving from one joint to another over a period of hours. ARF almost always affects the large joints—most commonly the knees, ankles, hips, and elbows—and is asymmetric. The pain is severe and usually disabling until anti-inflammatory medication is commenced.

Less severe joint involvement is also relatively common and has been recognized as a potential major manifestation in high-risk populations in the most recent revision of the Jones criteria. Arthralgia without

TABLE 32-1

WORLD HEART FEDERATION CRITERIA FOR ECHOCARDIOGRAPHIC DIAGNOSIS OF RHEUMATIC HEART DISEASE (RHD) IN INDIVIDUALS <20 YEARS OF AGE ^a	
Def nite RHD (either A, B, C, or D):	
(A)	Pathologic MR and at least two morphologic features of RHD of the mitral valve
(B)	MS mean gradient ≥4 mmHg (note: congenital MV anomalies must be excluded)
(C)	Pathologic AR and at least two morphologic features of RHD of the AV (note: bicuspid AV and dilated aortic root must be excluded)
(D)	Borderline disease of both the MV and AV
Borderline RHD (either A, B, or C):	
(A)	At least two morphologic features of RHD of the MV without pathologic MR or MS
(B)	Pathologic MR
(C)	Pathologic AR
Normal Echocardiographic Findings (all of A, B, C, and D):	
(A)	MR that does not meet all four Doppler criteria (physiologic MR)
(B)	AR that does not meet all four Doppler criteria (physiologic AR)
(C)	An isolated morphologic feature of RHD of the MV (e.g., valvular thickening), without any associated pathologic stenosis or regurgitation
(D)	Morphologic feature of RHD of the AV (e.g., valvular thickening), without any associated pathologic stenosis or regurgitation
Def nitions of Pathologic Regurgitation and Morphologic Features of RHD:	
Pathologic MR: All of the following: seen in two views; in at least one view, jet length 2 cm; peak velocity ≥3 m/s; pansystolic jet in at least one envelope	
Pathologic AR: All of the following: seen in two views; in at least one view, jet length ≥1 cm; peak velocity ≥3 m/s; pandiastolic jet in at least one envelope	
Morphologic features of RHD in MV: anterior MV leaflet thickening ≥3 mm (age specific); chordal thickening; restricted leaflet motion; excessive leaflet tip motion during systole	
Morphologic features of RHD in AV: irregular or focal thickening; coaptation defect; restricted leaflet motion; prolapse	

^aFor criteria in individuals >20 years of age, see source document.
Abbreviations: AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve.
Source: Adapted from Remenyi B et al: World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease-an evidence-based guideline. *Nat Rev Cardiol* 9:297–309, 2012.

objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis. In some populations, aseptic monoarthritis may be a presenting feature of ARF, which may, in turn, result from

early commencement of anti-inflammatory medication before the typical migratory pattern is established.

The joint manifestations of ARF are highly responsive to salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, joint involvement that persists for more than 1 or 2 days after starting salicylates is unlikely to be due to ARF.

CHOREA

Sydenham’s chorea commonly occurs in the absence of other manifestations, follows a prolonged latent period after group A streptococcal infection, and is found mainly in females. The choreiform movements affect particularly the head (causing characteristic darting movements of the tongue) and the upper limbs. They may be generalized or restricted to one side of the body (hemi-chorea). In mild cases, chorea may be evident only on careful examination, whereas in the most severe cases, the affected individuals are unable to perform activities of daily living. There is often associated emotional lability or obsessive-compulsive traits, which may last longer than the choreiform movements (which usually resolve within 6 weeks but sometimes may take up to 6 months).

SKIN MANIFESTATIONS

The classic rash of ARF is erythema marginatum, which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge. The rash is evanescent, appearing and disappearing before the examiner’s eyes. It occurs usually on the trunk, sometimes on the limbs, but almost never on the face.

Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skin overlying bony prominences, particularly of the hands, feet, elbows, occiput, and occasionally the vertebrae. They are a delayed manifestation, appearing 2–3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are commonly associated with carditis.

OTHER FEATURES

Fever occurs in most cases of ARF, although rarely in cases of pure chorea. Although high-grade fever (≥39°C) is the rule, lower grade temperature elevations are not uncommon. Elevated acute-phase reactants are also present in most cases.

EVIDENCE OF A PRECEDING GROUP A STREPTOCOCCAL INFECTION

With the exception of chorea and low-grade carditis, both of which may become manifest many months later, evidence of a preceding group A streptococcal

infection is essential in making the diagnosis of ARF. Because most cases do not have a positive throat swab culture or rapid antigen test, serologic evidence is usually needed. The most common serologic tests are the anti-streptolysin O (ASO) and anti-DNase B (ADB) titers. Where possible, age-specific reference ranges should be determined in a local population of healthy people without a recent group A streptococcal infection.

CONFIRMING THE DIAGNOSIS

Because there is no definitive test, the diagnosis of ARF relies on the presence of a combination of typical clinical features together with evidence of the precipitating group A streptococcal infection, and the exclusion of other diagnoses. This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the Jones criteria) to aid in the diagnosis. The most recent revision of the Jones criteria (Table 32-2) require the clinician to determine if the patient is from a setting or population known to experience low rates of ARF. For this group, there is a set of “low-risk” criteria; for all others, there is a set of more sensitive criteria.

TREATMENT Acute Rheumatic Fever

Patients with possible ARF should be followed closely to ensure that the diagnosis is confirmed, treatment of heart failure and other symptoms is undertaken, and preventive measures including commencement of secondary prophylaxis, inclusion on an ARF registry, and health education are commenced. Echocardiography should be performed on all possible cases to aid in making the diagnosis and to determine the severity at baseline of any carditis. Other tests that should be performed are listed in Table 32-3.

There is no treatment for ARF that has been proven to alter the likelihood of developing, or the severity of, RHD. With the exception of treatment of heart failure, which may be life-saving in cases of severe carditis, the treatment of ARF is symptomatic.

ANTIBIOTICS All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection. Penicillin is the drug of choice and can be given orally (as phenoxymethyl penicillin, 500 mg [250 mg for children ≤27 kg] PO twice daily, or amoxicillin, 50 mg/kg [maximum, 1 g] daily, for 10 days) or as a single dose of 1.2 million units (600,000 units for children ≤27 kg) IM benzathine penicillin G.

SALICYLATES AND NSAIDS These may be used for the treatment of arthritis, arthralgia, and fever, once the diagnosis is confirmed. They are of no proven value in the treatment of carditis or chorea. Aspirin is the drug of choice, delivered at a dose of

50–60 mg/kg per day, up to a maximum of 80–100 mg/kg per day (4–8 g/d in adults) in four to five divided doses. At higher doses, the patient should be monitored for symptoms of salicylate

TABLE 32-2

REVISED JONES CRITERIA, 2015	
DIAGNOSTIC CATEGORIES	CRITERIA
A. For all patient populations with evidence of preceding group A streptococcal infection	
Diagnosis: initial ARF	2 Major manifestations or 1 major plus 2 minor manifestations
Diagnosis: recurrent ARF	2 Major or 1 major and 2 minor or 3 minor
B. Major criteria	
Low-risk populations ^a	Moderate- and high-risk populations
Carditis ^b	Arthritis
• Clinical and/or subclinical Carditis	• Polyarthritis only
• Clinical and/or subclinical Carditis	Arthritis
• Clinical and/or subclinical Carditis	• Monoarthritis or polyarthritis
Chorea	Polyarthralgia ^c
Erythema marginatum	Chorea
SC nodules	Erythema marginatum
	SC nodules
C. Minor criteria	
Low-risk populations ^a	Moderate- and high-risk populations
Polyarthralgia	Monoarthralgia
Fever (≥38.5°C)	Fever (≥38°C)
ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL ^d	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL ^d
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

^aLow-risk populations are those with ARF incidence ≤2 per 100,000 school-age children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year.

^bSubclinical carditis indicates echocardiographic valvulitis. (See source document.)

^cPolyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and SC nodules are rarely “stand-alone” major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient. (See source document for more information.)

^dCRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.

Source: Gewitz MH et al: Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: A scientific statement from the American Heart Association. *Circulation* 131:1806, 2015.

TABLE 32-3

RECOMMENDED TESTS IN CASES OF POSSIBLE ACUTE RHEUMATIC FEVER	
Recommended for All Cases	
White blood cell count	
Erythrocyte sedimentation rate	
C-reactive protein	
Blood cultures if febrile	
Electrocardiogram (if prolonged P-R interval or other rhythm abnormality, repeat in 2 weeks and again at 2 months if still abnormal)	
Chest x-ray if clinical or echocardiographic evidence of carditis	
Echocardiogram (consider repeating after 1 month if negative)	
Throat swab (preferably before giving antibiotics)—culture for group A streptococcus	
Antistreptococcal serology: both anti-streptolysin O and anti-DNase B titers, if available (repeat 10–14 days later if first test not confirmatory)	
Tests for Alternative Diagnoses, Depending on Clinical Features	
Repeated blood cultures if possible endocarditis	
Joint aspirate (microscopy and culture) for possible septic arthritis	
Copper, ceruloplasmin, antinuclear antibody, drug screen for choreiform movements	
Serology and autoimmune markers for arboviral, autoimmune, or reactive arthritis	

Source: Reprinted with permission from Menzies School of Health Research (<http://www.rhdaustralia.org.au/arf-rhd-guideline>).

toxicity such as nausea, vomiting, or tinnitus; if symptoms appear, lower doses should be used. When the acute symptoms are substantially resolved, usually within the first 2 weeks, patients on higher doses can have the dose reduced to 50–60 mg/kg per day for a further 2–4 weeks. Fever, joint manifestations, and elevated acute-phase reactants sometimes recur up to 3 weeks after the medication is discontinued. This does not indicate a recurrence and can be managed by recommencing salicylates for a brief period. Naproxen at a dose of 10–20 mg/kg per day is a suitable alternative to aspirin and has the advantage of twice-daily dosing.

CONGESTIVE HEART FAILURE

Glucocorticoids The use of glucocorticoids in ARF remains controversial. Two meta-analyses have failed to demonstrate a benefit of glucocorticoids compared to placebo or salicylates in improving the short- or longer term outcome of carditis. However, the studies included in these meta-analyses all took place >40 years ago and did not use medications in common usage today. Many clinicians treat cases of severe carditis (causing heart failure) with glucocorticoids in the belief that they may reduce the acute inflammation and result in more rapid resolution of failure. However,

the potential benefits of this treatment should be balanced against the possible adverse effects. If used, prednisone or prednisolone is recommended at a dose of 1–2 mg/kg per day (maximum, 80 mg), usually for a few days or up to a maximum of 3 weeks.

MANAGEMENT OF HEART FAILURE

See chap. 20.

BED REST Traditional recommendations for long-term bed rest, once the cornerstone of management, are no longer widely practiced. Instead, bed rest should be prescribed as needed while arthritis and arthralgia are present and for patients with heart failure. Once symptoms are well controlled, gradual mobilization can commence as tolerated.

CHOREA Medications to control the abnormal movements do not alter the duration or outcome of chorea. Milder cases can usually be managed by providing a calm environment. In patients with severe chorea, carbamazepine or sodium valproate is preferred to haloperidol. A response may not be seen for 1–2 weeks, and medication should be continued for 1–2 weeks after symptoms subside. There is recent evidence that corticosteroids are effective and lead to more rapid symptom reduction in chorea. They should be considered in severe or refractory cases. Prednisone or prednisolone may be commenced at 0.5 mg/kg daily, with weaning as early as possible, preferably after 1 week if symptoms are reduced, although slower weaning or temporary dose escalation may be required if symptoms worsen.

INTRAVENOUS IMMUNOGLOBULIN (IVIg) Small studies have suggested that IVIg may lead to more rapid resolution of chorea but have shown no benefit on the short- or long-term outcome of carditis in ARF without chorea. In the absence of better data, IVIg is not recommended except in cases of severe chorea refractory to other treatments.

PROGNOSIS

Untreated, ARF lasts on average 12 weeks. With treatment, patients are usually discharged from hospital within 1–2 weeks. Inflammatory markers should be monitored every 1–2 weeks until they have normalized (usually within 4–6 weeks), and an echocardiogram should be performed after 1 month to determine if there has been progression of carditis. Cases with more severe carditis need close clinical and echocardiographic monitoring in the longer term.

Once the acute episode has resolved, the priority in management is to ensure long-term clinical follow-up and adherence to a regimen of secondary prophylaxis. Patients should be entered onto the local ARF registry (if present) and contact made with primary care practitioners to ensure a plan for follow-up and

administration of secondary prophylaxis before the patient is discharged. Patients and their families should also be educated about their disease, emphasizing the importance of adherence to secondary prophylaxis.

PREVENTION

PRIMARY PREVENTION

Ideally, primary prevention would entail elimination of the major risk factors for streptococcal infection, particularly overcrowded housing. This is difficult to achieve in most places where ARF is common.

Therefore, the mainstay of primary prevention for ARF remains primary prophylaxis (i.e., the timely and complete treatment of group A streptococcal sore throat with antibiotics). If commenced within 9 days of sore throat onset, a course of penicillin (as outlined above for treatment of ARF) will prevent almost all cases of ARF that would otherwise have developed. In settings where ARF and RHD are common but microbiologic diagnosis of group A streptococcal pharyngitis is not available, such as in resource-poor countries, primary care guidelines often recommend that all patients with sore throat be treated with penicillin or, alternatively, that a clinical algorithm be used to identify patients with a higher likelihood of group A streptococcal pharyngitis. Although imperfect, such approaches recognize the importance of ARF prevention at the expense of overtreating many cases of sore throat that are not caused by group A streptococcus.

SECONDARY PREVENTION

The mainstay of controlling ARF and RHD is secondary prevention. Because patients with ARF are at dramatically higher risk than the general population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences. The best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if ≤ 27 kg) delivered every 4 weeks. It can be given every 3 weeks, or even every 2 weeks, to persons considered to be at particularly high risk, although in settings where good compliance with an every-4-week dosing schedule can be achieved, more frequent dosing is rarely needed. Oral penicillin V (250 mg) can be given twice daily instead but is less effective than benzathine penicillin G. Penicillin-allergic patients can receive erythromycin (250 mg) twice daily.

The duration of secondary prophylaxis is determined by many factors, in particular the duration since the last episode of ARF (recurrences become less likely with

increasing time), age (recurrences are less likely with increasing age), and the severity of RHD (if severe, it may be prudent to avoid even a very small risk of recurrence because of the potentially serious consequences) (Table 32-4). Secondary prophylaxis is best delivered as part of a coordinated RHD control program, based around a registry of patients. Registries improve the ability to follow patients and identify those who default from prophylaxis and to institute strategies to improve adherence.

TABLE 32-4

AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR DURATION OF SECONDARY PROPHYLAXIS^a

CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Rheumatic fever without carditis	For 5 years after the last attack or 21 years of age (whichever is longer)
Rheumatic fever with carditis but no residual valvular disease	For 10 years after the last attack, or 21 years of age (whichever is longer)
Rheumatic fever with persistent valvular disease, evident clinically or on echocardiography	For 10 years after the last attack, or 40 years of age (whichever is longer); sometimes lifelong prophylaxis

^aThese are only recommendations and must be modified by individual circumstances as warranted. Note that some organizations recommend a minimum of 10 years of prophylaxis after the most recent episode, or until 21 years of age (whichever is longer), regardless of the presence of carditis with the initial episode.

Source: Adapted from AHA Scientific Statement Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis. *Circulation* 119:1541, 2009.

Videos can be accessed via the following link:

<https://www.mhprofessional.com/mediacenter/>.

Video 32-1 A Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever.

Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. The valve leaflets are relatively thin and highly mobile. The failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. The mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. A. Acute rheumatic carditis (apical four-chamber view echocardiogram).

Video 32-1 B Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever.

Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. The valve leaflets are relatively thin and highly mobile. The failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. The mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. B. Acute rheumatic carditis (apical four-chamber view color Doppler echocardiogram).

Video 32-1 C Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever.

Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. The valve leaflets are relatively thin and highly mobile. The failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. The mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. C. Acute rheumatic carditis (parasternal long-axis view echocardiogram).

Video 32-1 D Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever.

Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. The valve leaflets are relatively thin and highly mobile. The failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. The mitral valve

regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. D. Acute rheumatic carditis (parasternal long-axis view color Doppler echocardiogram).

Video 32-2 A Transthoracic echocardiographic images are from a 5-year-old boy with chronic rheumatic heart disease with severe mitral valve regurgitation and moderate mitral valve stenosis.

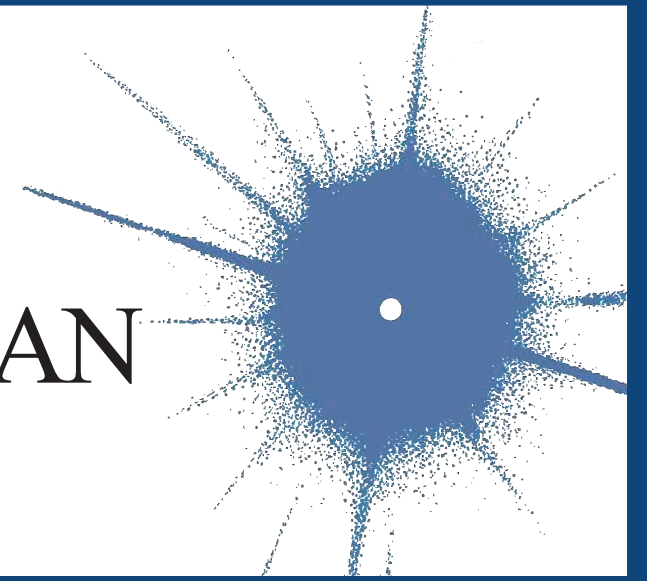
Images demonstrate the typical echocardiographic findings in advanced chronic rheumatic heart disease. Both the anterior and posterior mitral valve leaflets are markedly thickened. During diastole, the motion of the anterior mitral valve leaflet tip is restricted with doming of the body of the leaflet toward the interventricular septum. This appearance is commonly described as a “hockey stick” or an “elbow” deformity. A. Chronic rheumatic heart disease (parasternal long-axis view).

Video 32-2 B Transthoracic echocardiographic images are from a 5-year-old boy with chronic rheumatic heart disease with severe mitral valve regurgitation and moderate mitral valve stenosis.

Images demonstrate the typical echocardiographic findings in advanced chronic rheumatic heart disease. Both the anterior and posterior mitral valve leaflets are markedly thickened. During diastole, the motion of the anterior mitral valve leaflet tip is restricted with doming of the body of the leaflet toward the interventricular septum. This appearance is commonly described as a “hockey stick” or an “elbow” deformity. B. Chronic rheumatic heart disease (apical two-chamber view echocardiogram).

CHAPTER 33

CHAGAS DISEASE AND AFRICAN TRYPANOSOMIASIS



Louis V. Kirchhof ■ Anis Rassi, Jr.

Although the genus *Trypanosoma* contains many species of protozoans, only *T. cruzi*, *T. brucei gambiense*, and *T. brucei rhodesiense* cause disease in humans. *T. cruzi* is the etiologic agent of Chagas disease in the Americas; *T. b. gambiense* and *T. b. rhodesiense* cause African trypanosomiasis.

CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)

DEFINITION

Chagas disease, or American trypanosomiasis, is a zoonosis caused by the protozoan parasite *T. cruzi*. Acute Chagas disease is usually a mild febrile illness that results from initial infection with the organism. After spontaneous resolution of the acute illness, most infected persons remain for life in the indeterminate phase of chronic Chagas disease, which is characterized by subpatent parasitemia, easily detectable IgG antibodies to *T. cruzi*, and an absence of associated signs and symptoms. In 10–30% of chronically infected patients, cardiac and/or gastrointestinal symptoms develop that can lead to serious morbidity and even death.

LIFE CYCLE AND TRANSMISSION

T. cruzi is transmitted among its mammalian hosts by hematophagous triatomine insects, often called reduviid bugs. The insects become infected by sucking blood from animals or humans with circulating parasites. Ingested organisms multiply in the gut of the triatomines, and infective forms are discharged with the feces at the time of subsequent blood meals. Transmission to a second vertebrate host occurs when breaks in the skin, mucous membranes, or conjunctivae become contaminated with bug feces that contain infective parasites.

T. cruzi can also be transmitted by transfusion of blood donated by infected persons, by organ transplantation, from mother to unborn child, by ingestion of contaminated food or drink, and in laboratory accidents.

PATHOLOGY

Initial infection at the site of parasite entry is characterized by local histologic changes that include the presence of parasites within leukocytes and cells of subcutaneous tissues and the development of interstitial edema, lymphocytic infiltration, and reactive hyperplasia of adjacent lymph nodes. After dissemination of the organisms through the lymphatics and the bloodstream, primarily muscles (including the myocardium) (**Fig. 33-1**) and ganglion cells may become heavily parasitized.

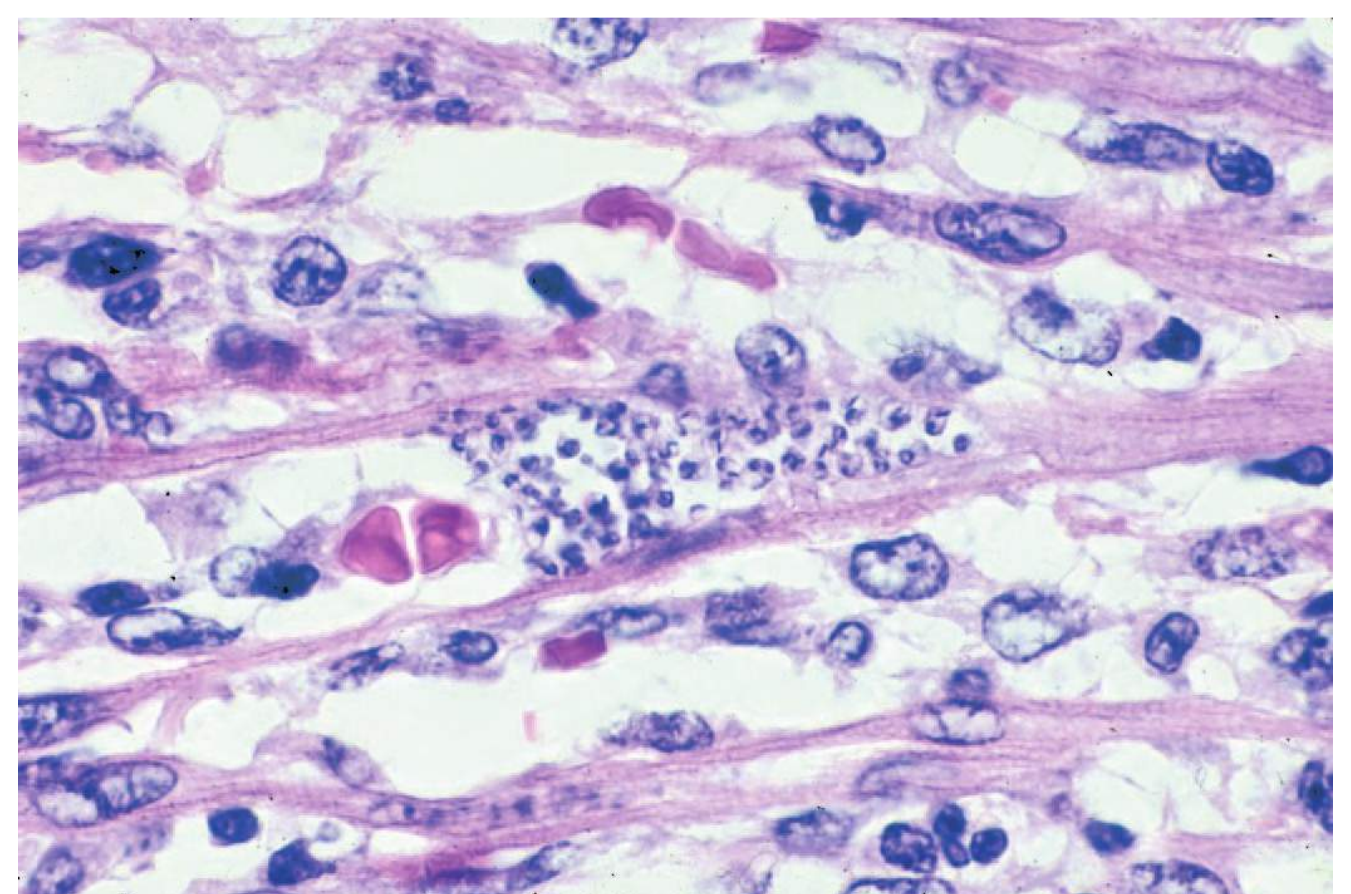


FIGURE 33-1

Trypanosoma cruzi in the heart muscle of a child who died of acute Chagas myocarditis. An infected myocyte containing several dozen *T. cruzi* amastigotes is in the center of the field (hematoxylin and eosin, 900 ×).

The characteristic pseudocysts present in sections of infected tissues are intracellular aggregates of multiplying parasites.

In persons with chronic *T. cruzi* infections who develop related clinical manifestations, the heart is the organ most commonly affected. Changes include thinning of the ventricular walls, biventricular enlargement, apical aneurysms, and mural thrombi. Widespread lymphocytic infiltration, diffuse interstitial fibrosis, and atrophy of myocardial cells are often apparent. Although parasites are difficult to find in myocardial tissue by conventional histologic methods, more sensitive techniques of parasite detection, such as immunohistochemistry and polymerase chain reaction (PCR), have more frequently demonstrated *T. cruzi* antigens and parasite DNA in chronic lesions. Conduction-system abnormalities often affect the right branch and the left anterior branch of the bundle of His. In chronic Chagas disease of the gastrointestinal tract (megadisease), the esophagus and colon may exhibit varying degrees of dilation. On microscopic examination, focal inflammatory lesions with lymphocytic infiltration are seen, and the number of neurons in the myenteric plexus may be markedly reduced. Accumulating evidence implicates the persistence of parasites and the accompanying chronic inflammation—rather than autoimmune mechanisms—as the basis for the pathology in patients with chronic *T. cruzi* infection.

EPIDEMIOLOGY



T. cruzi is found only in the Americas. Wild and domestic mammals harboring *T. cruzi* and infected triatomines are found in spotty distributions from the southern United States to southern Argentina. Humans become involved in the cycle of transmission when infected vectors take up residence in the primitive wood, adobe, and stone houses common in much of Latin America. Thus human *T. cruzi* infection is a health problem primarily among the poor in rural areas of Mexico and Central and South America. Most new *T. cruzi* infections in rural settings occur in children, but the incidence is unknown because most cases go undiagnosed. Historically, transfusion-associated transmission of *T. cruzi* was a serious public health problem in many endemic countries. Transmission by this route has been largely eliminated, however, as effective programs for serologic screening of donated blood have been implemented. Several dozen patients with HIV and chronic *T. cruzi* infections who underwent acute recrudescence of the latter have been described. These patients generally presented with *T. cruzi* brain abscesses, a manifestation of the illness that does not occur in immunocompetent persons. Currently, it is estimated that 8 million people are chronically infected with *T. cruzi* and that 14,000 deaths due to the illness

occur each year. The resulting morbidity and mortality make Chagas disease the most important parasitic disease burden in Latin America.

In recent years, the rate of *T. cruzi* transmission has decreased markedly in several endemic countries as a result of successful programs involving vector control, screening of donated blood, and education of at-risk populations. A major program, which began in 1991 in the “southern cone” nations of South America (Uruguay, Paraguay, Bolivia, Brazil, Chile, and Argentina), has provided the framework for much of this progress. Uruguay and Chile were certified free of transmission by the main domiciliary vector species (*Triatoma infestans*) in the late 1990s, and Brazil was declared transmission-free in 2006. Transmission has been reduced markedly in Argentina as well. Similar control programs have been initiated in the countries of northern South America and in the Central American nations.

Acute Chagas disease is rare in the United States, where 22 cases of autochthonous transmission and seven instances of transmission by blood transfusion have been reported. Moreover, *T. cruzi* was transmitted to five recipients of organs from three *T. cruzi*-infected donors, two of whom became infected through cardiac transplants. Acute Chagas disease has been reported in only one tourist returning to the United States from Latin America, although three such instances have been reported in Europe as well as one in Canada. In contrast, the prevalence of chronic *T. cruzi* infections in the United States has increased considerably in recent years. An estimated 23 million immigrants from Chagas-endemic countries currently live in the United States, ~17 million of whom are Mexicans. The total number of *T. cruzi*-infected persons living in the United States is estimated to be 300,000. Screening of the U.S. blood supply for *T. cruzi* infection began in January 2007. The overall prevalence of *T. cruzi* infection among donors is ~1 in 13,300, and to date nearly 3000 infected donors have been identified and deferred permanently (see “Diagnosis,” below).

CLINICAL COURSE

The first signs of acute Chagas disease develop at least 1 week after invasion by the parasites. When the organisms enter through a break in the skin, an indurated area of erythema and swelling (the chagoma), accompanied by local lymphadenopathy, may appear. Romaña sign—the classic finding in acute Chagas disease, which consists of unilateral painless edema of the palpebrae and periocular tissues—can result when the conjunctiva is the portal of entry. These initial local signs may be followed by malaise, fever, anorexia, and edema of the face and lower extremities. Generalized lymphadenopathy and hepatosplenomegaly may develop. Severe myocarditis develops rarely; most deaths in acute Chagas

disease are due to heart failure. Neurologic signs are not common, but meningoencephalitis occurs occasionally, especially in children <2 years old. Usually within 4–8 weeks, acute signs and symptoms resolve spontaneously in virtually all patients, with commencement of the asymptomatic or indeterminate form of chronic *T. cruzi* infection.

Symptomatic chronic Chagas disease becomes apparent years or even decades after the initial infection. The heart is commonly involved, and symptoms are caused by rhythm disturbances, segmental or dilated cardiomyopathy, and thromboembolism. Right bundle branch block is a common electrocardiographic abnormality, but other types of intraventricular and atrioventricular blocks, premature ventricular contractions, and tachy- and bradyarrhythmias occur frequently. Cardiomyopathy often results in biventricular heart failure, with a predominance of right-sided failure at advanced stages. Embolization of mural thrombi to the brain or other areas may take place. Sudden death is the main cause of death in Chagas heart disease; congestive heart failure and stroke are next most common. Patients with megaesophagus suffer from dysphagia, odynophagia, chest pain, and regurgitation. Aspiration can occur (especially during sleep) in patients with severe esophageal dysfunction, and repeated episodes of aspiration pneumonitis are common. Weight loss, cachexia, and pulmonary infection can result in death. Patients with megacolon are plagued by abdominal pain and chronic constipation, which predisposes to fecaloma formation. Advanced megacolon can cause obstruction, volvulus, septicemia, and death.

DIAGNOSIS

The diagnosis of acute Chagas disease requires the detection of parasites. Microscopic examination of fresh anticoagulated blood or the buffy coat is the simplest way to see the motile organisms. Parasites also can be seen in Giemsa-stained thin and thick blood smears. Microhematocrit tubes containing acridine orange as a stain can be used for the same purpose. When used repeatedly by experienced personnel, all of these methods yield positive results in a high proportion of cases of acute Chagas disease. Serologic testing does not play a major role in diagnosing acute Chagas disease. PCR assays often give positive results in infected patients in whom traditional parasitologic tests are negative, including infants with congenital Chagas disease.

Chronic Chagas disease is diagnosed by the detection of specific IgG antibodies that bind to *T. cruzi* antigens. Demonstration of the parasite is not of primary importance. In Latin America, ~30 assays are commercially available, including several based on recombinant antigens. Although these tests usually show good sensitivity and reasonable specificity, false-positive reactions

may occur—typically with samples from patients who have other infectious and parasitic diseases or autoimmune disorders. In addition, confirmatory testing has presented a persistent challenge. For these reasons, the World Health Organization recommends that specimens be tested in at least two assays and that well-characterized positive and negative comparison samples be included in each run. The Chagas radioimmune precipitation assay (RIPA), a highly sensitive and specific confirmatory method for detecting antibodies to *T. cruzi*, is approved under the Clinical Laboratory Improvement Amendment and available in the laboratory of one of the authors (L.V.K.). In 2006, the U.S. Food and Drug Administration (FDA) approved a test to screen blood and organ donors for *T. cruzi* infection (Ortho *T. cruzi* ELISA Test System; Ortho-Clinical Diagnostics, Raritan, NJ). Since January 2007, the vast majority of U.S. blood donors have been screened, and positive units have undergone confirmatory testing with the Chagas RIPA. A second test for donor screening was approved by the FDA in 2010 (Abbott PRISM®Chagas Assay; Abbott Laboratories, Abbott Park, IL), as was an enzyme strip assay (Abbott ESA Chagas) in 2011. The use of PCR assays to detect *T. cruzi* DNA in chronically infected persons has been studied extensively; unfortunately, the sensitivity of this approach has not been shown to be reliably greater than that of serology.

TREATMENT Chagas Disease

Therapy for Chagas disease is still unsatisfactory. For many years now, only two drugs—nifurtimox and benznidazole—have been available for this purpose. Regrettably, both drugs lack efficacy and may cause bothersome side effects.

In acute Chagas disease, nifurtimox markedly reduces the duration of symptoms and parasitemia and decreases the mortality rate. Nevertheless, limited studies have shown that only ~70% of acute infections are cured by a full course of treatment. Common adverse effects of nifurtimox include anorexia, nausea, vomiting, weight loss, and abdominal pain. Neurologic reactions to the drug may include restlessness, disorientation, insomnia, twitching, paresthesia, polyneuritis, and seizures. These symptoms usually disappear when the dosage is reduced or treatment is discontinued. The recommended daily dosage is 8–10 mg/kg for adults, 12.5–15 mg/kg for adolescents, and 15–20 mg/kg for children 1–10 years of age. The drug should be given orally in four divided doses each day, and therapy should be continued for 90–120 days. Nifurtimox is available from the Drug Service of the Centers for Disease Control and Prevention (CDC) in Atlanta (telephone number, 404-639-3670).

The efficacy of benznidazole is similar or even superior to that of nifurtimox. A cure rate of >90% among congenitally infected infants treated before their first birthday has been reported. Adverse effects include rash, peripheral neuropathy,

and rare instances of granulocytopenia. The recommended oral dosage is 5 mg/kg per day for 60 days for adults and 5–10 mg/kg per day for 60 days for children, with administration of two or three divided doses. Benznidazole is generally considered the drug of choice in Latin America.



The question of whether adults in the indeterminate or chronic symptomatic phase of Chagas disease should be treated with nifurtimox or benznidazole has been debated for years. The fact that cure rates in persons with long-established chronic infection are notably inferior to those in patients with acute or recent chronic infection is central to this controversy. No convincing evidence from randomized controlled trials indicates that nifurtimox or benznidazole treatment of adults in the indeterminate or chronic symptomatic phase reduces either the appearance or progression of symptoms or mortality rates. On the basis of results of some observational studies, a panel of experts convened by the CDC in 2006 recommended that adults <50 years old with presumably longstanding indeterminate *T. cruzi* infections—or even with mild to moderate disease—be offered treatment. A large randomized clinical trial (the BENEFIT multicenter trial) designed to assess the parasitologic and clinical efficacy of benznidazole in 2856 adults (18–75 years old) with chronic Chagas heart disease (without advanced lesions) is being performed in Brazil, Argentina, Colombia, Bolivia, and El Salvador, but results will not be available until 2015. In contrast, randomized studies have shown that treatment of children is useful, and the current consensus of Latin American authorities and the CDC panel of experts is that all *T. cruzi*-infected persons up to 18 years old and all adults known to have become infected recently should be given benznidazole or nifurtimox.

The usefulness of antifungal azoles for the treatment of Chagas disease has been studied in laboratory animals and to a lesser extent in humans. To date, none of these drugs has exhibited a level of anti-*T. cruzi* activity that would justify its use in humans. Several newer drugs in this class have shown promise in animal studies and are currently being evaluated in phase 2 clinical trials.

Patients who develop cardiac and/or gastrointestinal disease in association with *T. cruzi* infection should be referred to appropriate subspecialists for further evaluation and treatment. Pacemakers can be useful in patients with ominous arrhythmias. The usefulness of implantable cardioverter defibrillators in persons with Chagas heart disease has not been established and currently is being studied in a prospective randomized trial. Cardiac transplantation is an option for patients with end-stage chagasic cardiomyopathy; more than 150 such transplantations have been done in Brazil and the United States. The survival rate among Chagas disease cardiac transplant recipients seems to be higher than that among persons receiving cardiac transplants for other reasons. This better outcome may be due to the fact that lesions are limited to the heart in most patients with symptomatic chronic Chagas disease.

PREVENTION



Because drug therapy has limitations and vaccines are not available, the control of *T. cruzi* transmission in endemic countries depends on the reduction of domiciliary vector populations by spraying of insecticides, improvements in housing, and education of at-risk persons. As noted above, these measures, coupled with serologic screening of blood donors, have markedly reduced transmission of the parasite in many endemic countries. Tourists would be wise to avoid sleeping in dilapidated houses in rural areas of endemic countries. Mosquito nets and insect repellent can provide additional protection.

In view of the possibly serious consequences of chronic *T. cruzi* infection, it would be prudent for all immigrants from endemic regions who are living in the United States to be tested for evidence of infection. Identification of persons harboring the parasite would permit periodic electrocardiographic monitoring, which is important to detect incipient heart disease and guide further diagnostic studies and treatment. The possibility of congenital transmission is yet another justification for screening. *T. cruzi* is classified as a Risk Group 2 agent in the United States and a Risk Group 3 agent in some European countries. Laboratory staff should work with the parasite or infected vectors and mammals at containment levels consistent with the risk group designation in their areas.

SLEEPING SICKNESS (AFRICAN TRYPANOSOMIASIS)

DEFINITION

Sleeping sickness, or human African trypanosomiasis (HAT), is caused by flagellated protozoan parasites that belong to the *T. brucei* complex and are transmitted to humans by tsetse flies. In untreated patients, the trypanosomes first cause a febrile illness that is followed months or years later by progressive neurologic impairment and death.

THE PARASITES AND THEIR TRANSMISSION

The East African (*rhodesiense*) and the West African (*gambiense*) forms of sleeping sickness are caused, respectively, by two trypanosome subspecies: *T. b. rhodesiense* and *T. b. gambiense*. These subspecies are morphologically indistinguishable but cause illnesses that are epidemiologically and clinically distinct (Table 33-1). The parasites are transmitted by blood-sucking tsetse flies of the genus *Glossina*. The insects acquire the infection when they ingest blood from infected mammalian hosts. After many cycles of multiplication in the midgut

TABLE 33-1

COMPARISON OF WEST AFRICAN AND EAST AFRICAN TRYPANOSOMIASIS

POINT OF COMPARISON	WEST AFRICAN (GAMBIENSE)	EAST AFRICAN (RHODESIENSE)
Organism	<i>T. b. gambiense</i>	<i>T. b. rhodesiense</i>
Vectors	Tsetse flies (palpalis group)	Tsetse flies (morsitans group)
Primary reservoir	Humans	Antelope and cattle
Human illness	Chronic (late CNS disease)	Acute (early CNS disease)
Duration of illness	Months to years	<9 months
Lymphadenopathy	Prominent	Minimal
Parasitemia	Low	High
Epidemiology	Rural populations	Workers in wild areas, rural populations, tourists in game parks

Abbreviation: CNS, central nervous system.

Source: Reprinted with permission from LV Kirchhof, in GL Mandell et al (eds): Principles and Practice of Infectious Diseases, 7th ed. Philadelphia, Elsevier Churchill Livingstone, 2010.

of the vector, the parasites migrate to the salivary glands. Their transmission takes place when they are inoculated into a mammalian host during a subsequent blood meal. The injected trypanosomes multiply in the blood (Fig. 33-2) and other extracellular spaces and evade immune destruction for long periods by undergoing antigenic variation, a process driven by gene switching

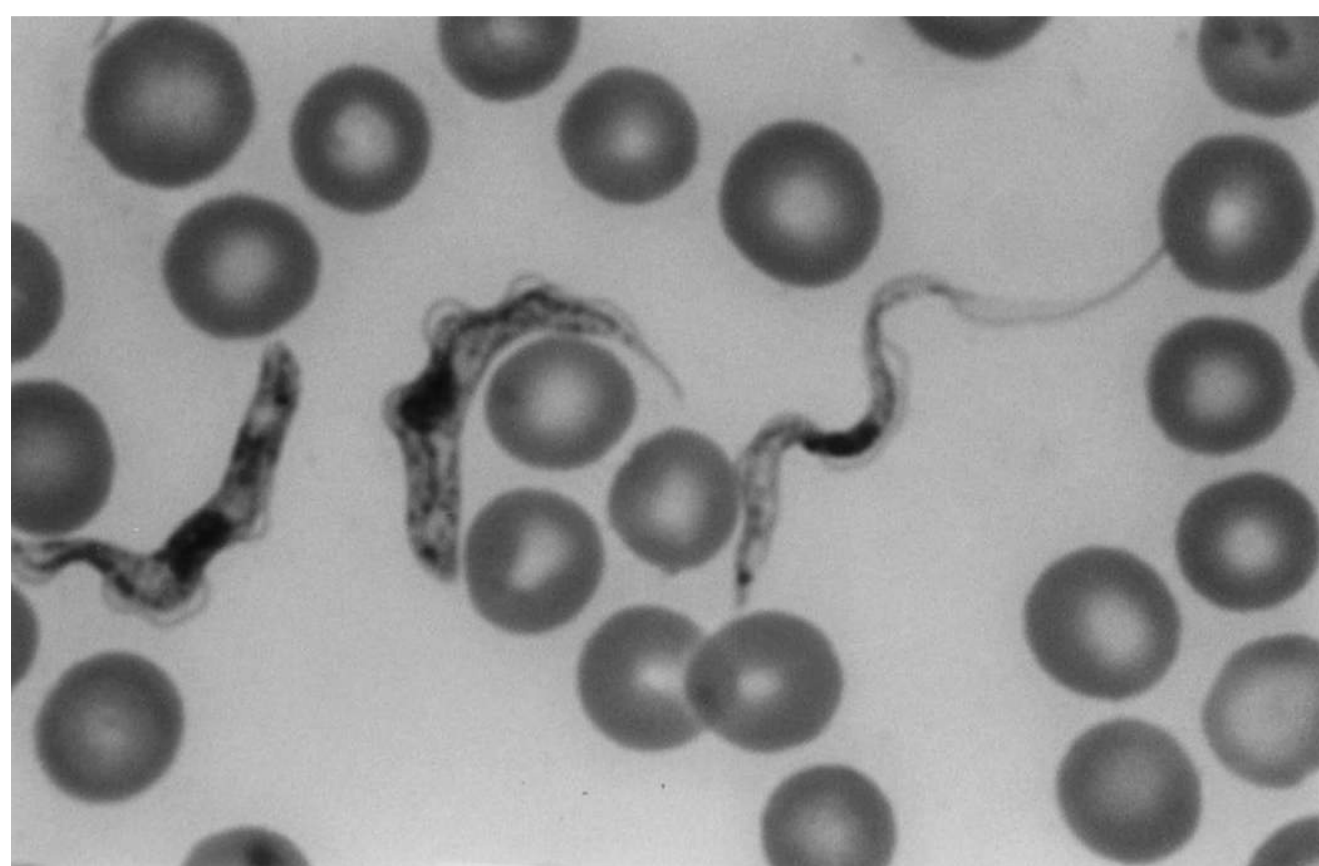


FIGURE 33-2

Trypanosoma brucei rhodesiense parasites in rat blood. The slender parasite is thought to be the form that multiplies in mammalian hosts, whereas the stumpy forms are nondividing and are capable of infecting insect vectors (Giemsa, 1200 ×). (Courtesy of Dr. G. A. Cook, Madison, WI; with permission.)

in which the antigenic structure of the organisms' surface coat of glycoproteins changes periodically.

PATHOGENESIS AND PATHOLOGY

A self-limited inflammatory lesion (trypanosomal chancre) may appear a week or so after the bite of an infected tsetse fly. A systemic febrile illness then evolves as the parasites are disseminated through the lymphatics and bloodstream. Systemic HAT without central nervous system (CNS) involvement is generally referred to as stage 1 disease. In this stage, widespread lymphadenopathy and splenomegaly reflect marked lymphocytic and histiocytic proliferation and invasion of morular cells, which are plasmacytes that may be involved in the production of IgM. Endarteritis, with perivascular infiltration of both parasites and lymphocytes, may develop in lymph nodes and the spleen. Myocarditis develops frequently in patients with stage 1 disease and is especially common in *T. b. rhodesiense* infections.

Hematologic manifestations that accompany stage 1 HAT include moderate leukocytosis, thrombocytopenia, and anemia. High levels of immunoglobulins, consisting primarily of polyclonal IgM, are a constant feature, and heterophile antibodies, antibodies to DNA, and rheumatoid factor are often detected. High levels of antigen-antibody complexes may play a role in the tissue damage and increased vascular permeability that facilitate dissemination of the parasites.

Stage 2 disease involves invasion of the CNS. The presence of trypanosomes in perivascular areas is accompanied by intense infiltration of mononuclear cells. Abnormalities in cerebrospinal fluid (CSF) include increased pressure, elevated total protein concentration, and pleocytosis. In addition, trypanosomes are frequently found in CSF.

EPIDEMIOLOGY



The trypanosomes that cause sleeping sickness are found only in sub-Saharan Africa. After its near-eradication in the mid-1960s, sleeping sickness underwent a resurgence in the 1990s, primarily in Uganda, Sudan, the Central African Republic, the Democratic Republic of the Congo, and Angola. A subsequent increase in control activities reduced the incidence in many endemic areas, however, and in 2009 fewer than 10,000 cases were reported to the World Health Organization. Although underreporting is a persistent problem, the level of control achieved to date was the basis for convening a panel of experts in 2009 to develop a vision for eradication of HAT.

Humans are the only reservoir of *T. b. gambiense*, which occurs in widely distributed foci in tropical rain forests of Central and West Africa. Gambiense

trypanosomiasis is primarily a problem in rural populations; tourists rarely become infected. Trypanotolerant antelope species in savanna and woodland areas of Central and East Africa are the principal reservoir of *T. b. rhodesiense*. Cattle can also be infected with this and other trypanosome species but generally succumb to the infection. Because risk results from contact with tsetse flies that feed on wild animals, humans acquire *T. b. rhodesiense* infection only incidentally, usually while visiting or working in areas where infected game and vectors are present. Roughly one or two imported cases of HAT acquired in East African parks are reported to the CDC each year.

CLINICAL COURSE

A painful trypanosomal chancre appears in some patients at the site of inoculation of the parasite. Hematogenous and lymphatic dissemination (stage 1 disease) is marked by the onset of fever. Typically, bouts of high temperatures lasting several days are separated by afebrile periods. Lymphadenopathy is prominent in *T. b. gambiense* trypanosomiasis. The nodes are discrete, movable, rubbery, and nontender. Cervical nodes are often visible, and enlargement of the nodes of the posterior cervical triangle, or Winterbottom's sign, is a classic finding. Pruritus and maculopapular rashes are common. Inconstant findings include malaise, headache, arthralgias, weight loss, edema, hepatosplenomegaly, and tachycardia. The differential diagnosis of stage 1 HAT includes many diseases that are common in the tropics and are associated with fevers. HIV infection, malaria, and typhoid fever are common in populations at risk for HAT and need to be considered.

CNS invasion (stage 2 disease) is characterized by the insidious development of protean neurologic manifestations that are accompanied by progressive abnormalities in the CSF. A picture of progressive indifference and daytime somnolence develops (hence the designation "sleeping sickness"), sometimes alternating with restlessness and insomnia at night. A listless gaze accompanies a loss of spontaneity, and speech may become halting and indistinct. Extrapyrimal signs may include choreiform movements, tremors, and fasciculations. Ataxia is frequent, and the patient may appear to have Parkinson's disease, with a shuffling gait, hypertonia, and tremors. In the final phase, progressive neurologic impairment ends in coma and death.

The most striking difference between the gambiense and rhodesiense forms of HAT is that the latter illness tends to follow a more acute course. Typically, in tourists with *T. b. rhodesiense* disease, systemic signs of infection, such as fever, malaise, and headache, appear before the end of the trip or shortly after the return home. Persistent tachycardia unrelated to fever is common early in the course of *T. b. rhodesiense* trypanosomiasis,

and death may result from arrhythmias and congestive heart failure before CNS disease develops. In general, untreated *T. b. rhodesiense* trypanosomiasis leads to death in a matter of weeks to months, often without a clear distinction between the hemolymphatic and CNS stages. In contrast, *T. b. gambiense* disease can smolder for many months or even for years.

DIAGNOSIS

A definitive diagnosis of HAT requires detection of the parasite. If a chancre is present, fluid should be expressed and examined directly by light microscopy for the highly motile trypanosomes. The fluid also should be fixed and stained with Giemsa. Material obtained by needle aspiration of lymph nodes early in the illness should be examined similarly. Examination of wet preparations and Giemsa-stained thin and thick films of serial blood samples is also useful. If parasites are not seen initially in blood, efforts should be made to concentrate the organisms, which can be done in microhematocrit tubes containing acridine orange. Alternatively, the buffy coat from 10–15 mL of anticoagulated blood can be examined directly under a microscope. The likelihood of finding parasites in blood is higher in stage 1 than in stage 2 disease and in patients infected with *T. b. rhodesiense* rather than *T. b. gambiense*. Trypanosomes may also be seen in material aspirated from the bone marrow; the aspirate can be inoculated into liquid culture medium, as can blood, buffy coat, lymph node aspirates, and CSF. It is essential to examine CSF from all patients in whom HAT is suspected. Abnormalities in the CSF that may be associated with stage 2 disease include an increase in the CSF cell count as well as increases in opening pressure and in levels of total protein and IgM. Trypanosomes may be seen in the sediment of centrifuged CSF. Any CSF abnormality in a patient in whom trypanosomes have been found at other sites must be viewed as pathognomonic for CNS involvement and thus must prompt specific treatment for CNS disease. In patients with CSF pleocytosis in whom parasites are not found, tuberculous meningitis and HIV-associated CNS infections such as cryptococcosis should be considered in the differential diagnosis.

A number of serologic assays, such as the card agglutination test for trypanosomes (CATT) for *T. b. gambiense*, are available to aid in the diagnosis of HAT. Their ease of use makes them valuable for epidemiologic surveys, but their variable sensitivity and specificity mandate that decisions about treatment be based on demonstration of the parasite. Accurate PCR assays for detecting African trypanosomes in humans have been developed, but the lack of the necessary technical and human resources in most endemic areas stands in the way of their widespread use.

TREATMENT Sleeping Sickness

The drugs used for treatment of HAT are suramin, pentamidine, eflornithine, and the organic arsenical melarsoprol. In the United States, these drugs can be obtained from the CDC. Therapy for HAT must be individualized on the basis of the infecting subspecies, the presence or absence of CNS disease, adverse reactions, and occasionally drug resistance. The choices of drugs for the treatment of HAT are summarized in **Table 33-2**.

Suramin is highly effective against stage 1 rhodesiense HAT. However, it can cause serious adverse effects and must be administered under the close supervision of a physician. A 100- to 200-mg IV test dose should be given to detect hypersensitivity. The dosage for adults is 20 mg/kg on days 1, 5, 12, 18, and 26. The drug is given by slow IV infusion of a freshly prepared 10% aqueous solution. Approximately 1 patient in 20,000 has an immediate, severe, and potentially fatal reaction to the drug, developing nausea, vomiting, shock, and seizures. Less severe reactions include fever, photophobia, pruritus, arthralgias, and skin eruptions. Renal damage is the most common important adverse effect of suramin. Transient proteinuria often appears during treatment. A urinalysis should be done before each dose, and treatment should be discontinued if proteinuria increases or if casts and red cells appear in the sediment. Suramin should not be given to patients with renal insufficiency.

Pentamidine is the first-line drug for treatment of stage 1 gambiense HAT. The dose for both adults and children is 4 mg/kg per day, given IM or IV for 7–10 days. Frequent, immediate adverse reactions include nausea, vomiting, tachycardia, and hypotension. These reactions are usually transient and do not warrant cessation of therapy. Other adverse reactions include nephrotoxicity, abnormal liver function tests,

neutropenia, rashes, hypoglycemia, and sterile abscesses. Suramin is an alternative agent for stage 1 *T. b. gambiense* disease.

Eflornithine is highly effective for treatment of both stages of gambiense sleeping sickness. In the trials on which the FDA based its approval, this agent cured >90% of 600 patients with stage 2 disease. The recommended treatment schedule is 400 mg/kg per day, given IV in four divided doses, for 2 weeks. Adverse reactions include diarrhea, anemia, thrombocytopenia, seizures, and hearing loss. The high dosage and duration of therapy required are disadvantages that make widespread use of eflornithine difficult. A randomized trial comparing the standard eflornithine regimen (400 mg/kg per day infused over 6 h for 14 days) with nifurtimox-eflornithine combination therapy (NECT; oral nifurtimox, 15 mg/kg per day in three divided doses, plus IV eflornithine, 200 mg/kg per day in two divided doses, both for 7 days) in adults with stage 2 gambiense HAT showed improved efficacy and reduced adverse effects with combination therapy, making this drug suitable for first-line use.

The arsenical melarsoprol is the drug of choice for the treatment of rhodesiense HAT with CNS involvement and is an alternative agent for stage 2 gambiense disease. The “short course” of melarsoprol that is currently recommended has been shown to be noninferior to the decades-old treatment course for *T. b. rhodesiense*, which was administered over several weeks and was much more toxic. The short-course regimen consists of 10 daily doses of 2.2 mg/kg IV, each given with prednisolone (1 mg/kg).

Melarsoprol is highly toxic and should be administered with great care. As noted, all patients receiving melarsoprol should be given prednisolone to reduce the likelihood of drug-induced encephalopathy. Without prednisolone prophylaxis, the incidence of reactive encephalopathy has been as high as 18% in some series. Clinical manifestations of reactive encephalopathy include high fever, headache, tremor, impaired speech, seizures, and even coma and death. Treatment with melarsoprol should be discontinued at the first sign of encephalopathy but may be restarted cautiously at lower doses a few days after signs have resolved. Extravasation of the drug results in intense local reactions. Vomiting, abdominal pain, nephrotoxicity, and myocardial damage can occur.

TABLE 33-2

TREATMENT OF HUMAN AFRICAN TRYPA NOSOMIASIS^a

CAUSATIVE ORGANISM	CLINICAL STAGE	
	1 (NORMAL CSF)	2 (ABNORMAL CSF)
T. b. gambiense (West African)	Pentamidine	Eflornithine
	Alternative: Suramin	Alternatives: NECT Melarsoprol ^b
T. b. rhodesiense (East African)	Suramin	Melarsoprol ^b
	Alternative: Pentamidine	

^aFor doses and duration, see text.

^bShort course.

Abbreviations: CSF, cerebrospinal fluid; NECT, nifurtimox-eflornithine combination therapy.

PREVENTION

HAT poses complex public-health and epizootic problems in Africa. Considerable progress has been made in many areas through control programs that focus on eradication of vectors and drug treatment of infected humans. People can reduce their risk of acquiring trypanosomiasis by avoiding areas known to harbor infected insects, by wearing protective clothing, and by using insect repellent. Chemoprophylaxis is not recommended, and no vaccine is available to prevent transmission of the parasites.

CHAPTER 34

CARDIOGENIC SHOCK AND PULMONARY EDEMA

Judith S. Hochman ■ David H. Ingbar

Cardiogenic shock and pulmonary edema are life-threatening conditions that should be treated as medical emergencies. The most common joint etiology is severe left ventricular (LV) dysfunction that leads to pulmonary congestion and/or systemic hypoperfusion (**Fig. 34-1**). The pathophysiology of pulmonary edema is discussed in Chap. 5.

CARDIOGENIC SHOCK

Cardiogenic shock (CS) is characterized by systemic hypoperfusion due to severe depression of the cardiac index (<2.2 [L/min]/m²) and sustained systolic arterial hypotension (<90 mmHg) despite an elevated filling pressure (pulmonary capillary wedge pressure [PCWP] >18 mmHg). It is associated with in-hospital mortality rates $>50\%$. The major causes of CS are listed in **Table 34-1**. Circulatory failure based on cardiac dysfunction may be caused by primary myocardial failure, most commonly secondary to acute myocardial infarction (MI) (**Chap. 41**), and less frequently by cardiomyopathy or myocarditis (**Chap. 27**), cardiac tamponade (**Chap. 28**), or critical valvular heart disease (**Chap. 23**).

Incidence

The rate of CS complicating acute MI was 20% in the 1960s, stayed at $\sim 8\%$ for >20 years, but decreased to 5–7% in the first decade of this millennium largely due to increasing use of early reperfusion therapy for acute MI. Shock is more common with ST elevation MI (STEMI) than with non-ST elevation MI (**Chap. 41**).

LV failure accounts for $\sim 80\%$ of cases of CS complicating acute MI. Acute severe mitral regurgitation (MR), ventricular septal rupture (VSR), predominant right ventricular (RV) failure, and free wall rupture or tamponade account for the remainder.

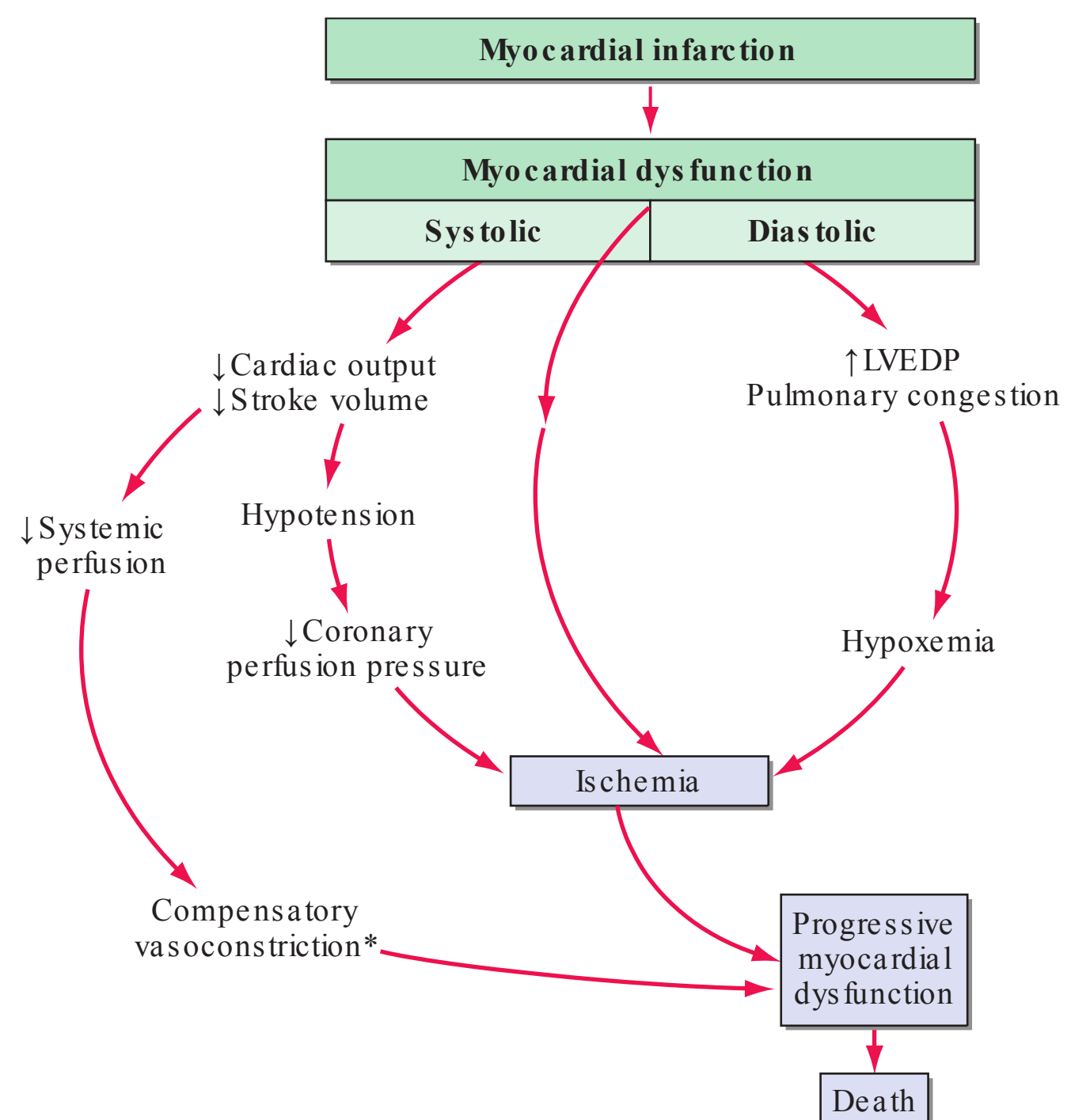


FIGURE 34-1

Pathophysiology of cardiogenic shock. Systolic and diastolic myocardial dysfunction results in a reduction in cardiac output and often pulmonary congestion. Systemic and coronary hypoperfusion occur, resulting in progressive ischemia. Although a number of compensatory mechanisms are activated in an attempt to support the circulation, these compensatory mechanisms may become maladaptive and produce a worsening of hemodynamics. *Release of inflammatory cytokines after myocardial infarction may lead to inducible nitric oxide expression, excess nitric oxide, and inappropriate vasodilation. This causes further reduction in systemic and coronary perfusion. A vicious spiral of progressive myocardial dysfunction occurs that ultimately results in death if it is not interrupted. LVEDP, left ventricular end-diastolic pressure. (From SM Hollenberg et al: *Ann Intern Med* 131:47, 1999.)

TABLE 34-1

ETIOLOGIES OF CARADIOGENIC SHOCK (CS) ^a AND CARADIOGENIC PULMONARY EDEMA
ETIOLOGIES OF CARADIOGENIC SHOCK OR PULMONARY EDEMA
Acute myocardial infarction/ischemia
LV failure
Ventricular septal rupture
Papillary muscle/chordal rupture—severe MR
Ventricular free wall rupture with subacute tamponade
Other conditions complicating large MIs
Hemorrhage
Infection
Excess negative inotropic or vasodilator medications
Prior valvular heart disease
Hyperglycemia/ketoacidosis
Post-cardiac arrest
Post-cardiotomy
Refractory sustained tachyarrhythmias
Acute fulminant myocarditis
End-stage cardiomyopathy
LV apical ballooning
Takotsubo’s cardiomyopathy
Hypertrophic cardiomyopathy with severe outflow obstruction
Aortic dissection with aortic insufficiency or tamponade
Severe valvular heart disease
Critical aortic or mitral stenosis
Acute severe aortic regurgitation or mitral regurgitation
Toxic/metabolic
β blocker or calcium channel antagonist overdose
Other Etiologies of Cardiogenic Shock^b
RV failure due to:
Acute myocardial infarction
Acute cor pulmonale
Refractory sustained bradyarrhythmias
Pericardial tamponade
Toxic/metabolic
Severe acidosis, severe hypoxemia

^aThe etiologies of CS are listed. Most of these can cause pulmonary edema instead of shock or pulmonary edema with CS.
^bThese cause CS but not pulmonary edema.
Abbreviations: LV, left ventricular; MI, myocardial infarction; MR, mitral regurgitation; RV, right ventricular; VSR, ventricular septal rupture.

Pathophysiology

CS is characterized by a vicious circle in which depression of myocardial contractility, usually due to ischemia, results in reduced cardiac output and arterial

blood pressure (BP), which result in hypoperfusion of the myocardium and further ischemia and depression of cardiac output (Fig. 34-1). Systolic myocardial dysfunction reduces stroke volume and, together with diastolic dysfunction, leads to elevated LV end-diastolic pressure and PCWP as well as to pulmonary congestion. Reduced coronary perfusion leads to worsening ischemia and progressive myocardial dysfunction and a rapid downward spiral, which, if uninterrupted, is often fatal. A systemic inflammatory response syndrome may accompany large infarctions and shock. Inflammatory cytokines, inducible nitric oxide synthase, and excess nitric oxide and peroxynitrite may contribute to the genesis of CS as they do to that of other forms of shock. Lactic acidosis and hypoxemia from CS contribute to the vicious circle by worsening myocardial ischemia and hypotension. Severe acidosis reduces the efficacy of endogenous and exogenously administered catecholamines. Refractory sustained ventricular or atrial tachyarrhythmias can cause or exacerbate CS.

Patient profile

Older age, female sex, prior MI, diabetes, anterior MI location, and extensive coronary artery stenoses are associated with an increased risk of CS complicating MI. Shock associated with a first inferior MI should prompt a search for a mechanical cause. CS may rarely occur in the absence of significant stenosis, as seen in LV apical ballooning/Takotsubo’s cardiomyopathy.

Timing

Shock is present on admission in only one-quarter of patients who develop CS complicating MI; one-quarter develop it rapidly thereafter, within 6 h of MI onset. Another quarter develop shock later on the first day. Subsequent onset of CS may be due to reinfarction, marked infarct expansion, or a mechanical complication.

Diagnosis

Due to the unstable condition of these patients, supportive therapy must be initiated simultaneously with diagnostic evaluation (Fig. 34-2). A focused history and physical examination should be performed, blood specimens sent to the laboratory, and an electrocardiogram (ECG) and chest x-ray obtained.

Echocardiography is an invaluable diagnostic tool in patients with suspected CS.

Clinical findings

Most patients have dyspnea and appear pale, apprehensive, and diaphoretic, and mental status may be altered. The pulse is typically weak and rapid, often in the range of 90–110 beats/min, or severe bradycardia due

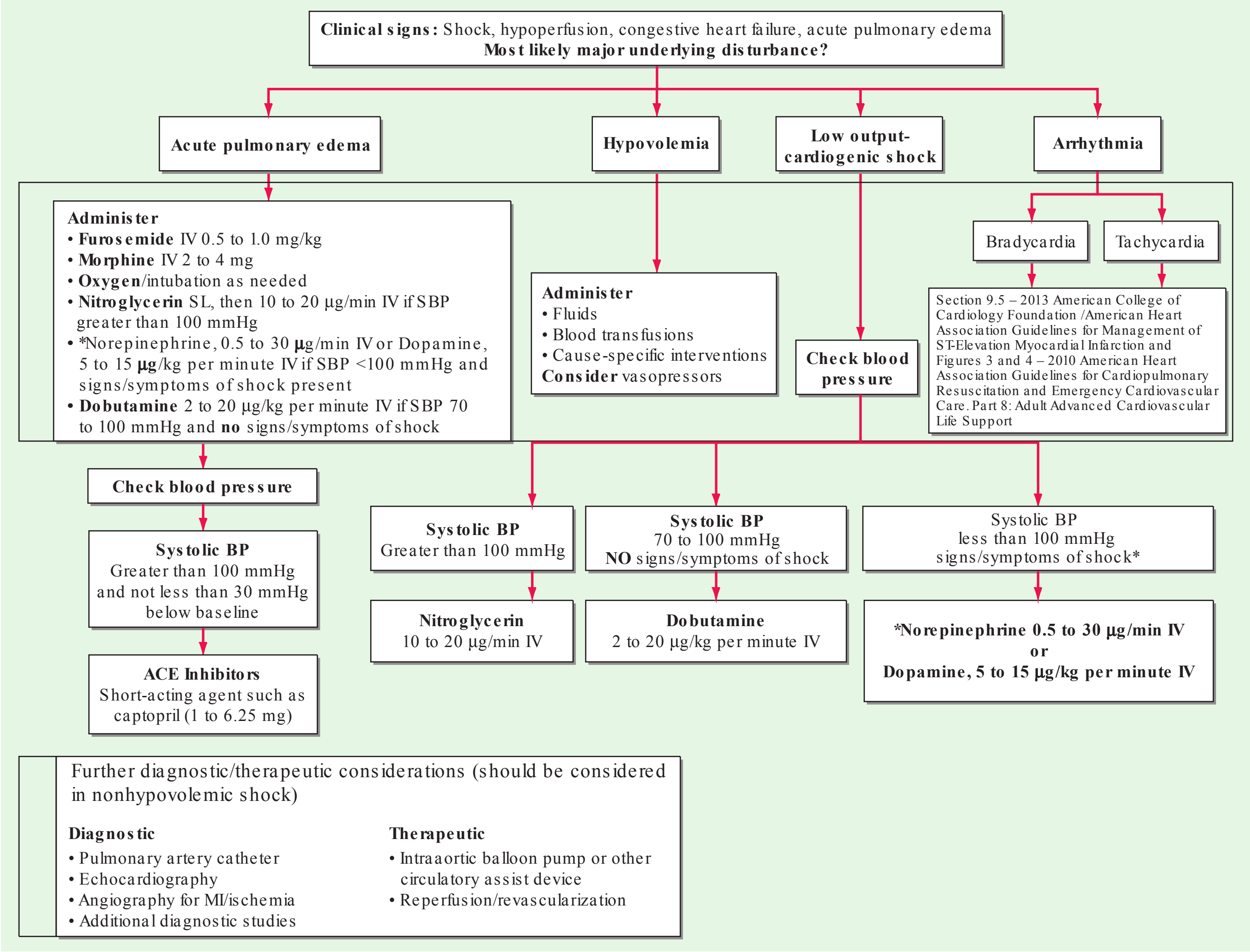


FIGURE 34-2

The emergency management of patients with cardiogenic shock, acute pulmonary edema, or both is outlined.

*Furosemide: <0.5 mg/kg for new-onset acute pulmonary edema without hypervolemia; 1 mg/kg for acute on chronic volume overload, renal insufficiency.

†For management of bradycardia and tachycardia, see **Chaps. 15 and 17**. Additional information can also be found in Section 9.5 of the 2013 American College of Cardiology Foundation/American Heart Association Guidelines for Management of ST-Elevation Myocardial Infarction and Figures 3 and 4 of the 2010 American Heart Association Guidelines for Cardiopulmonary

to high-grade heart block may be present. Systolic BP is reduced (<90 mmHg or ≥30 mmHg below baseline) with a narrow pulse pressure (<30 mmHg), but occasionally BP may be maintained by very high systemic vascular resistance. Tachypnea, Cheyne-Stokes respirations, and jugular venous distention may be present. There is typically a weak apical pulse and soft S₁, and an S₃ gallop may be audible. Acute, severe MR and VSR usually are associated with characteristic systolic murmurs (**Chap. 41**). Rales are audible in most patients with LV failure. Oliguria is common.

Resuscitation and Emergency Cardiovascular Care. Part 8: Adult Advanced Cardiovascular Life Support.

*Indicates modification from published guidelines. ACE, angiotensin-converting enzyme; BP, blood pressure; MI, myocardial infarction. (Modified from Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7: The era of reperfusion: Section 1: Acute coronary syndromes [acute myocardial infarction]. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 102:II72, 2000.)

Laboratory findings

The white blood cell count is typically elevated with a left shift. Renal function is initially unchanged, but blood urea nitrogen and creatinine rise progressively. Hepatic transaminases may be markedly elevated due to liver hypoperfusion. The lactic acid level is elevated. Arterial blood gases usually demonstrate hypoxemia and anion gap metabolic acidosis, which may be compensated by respiratory alkalosis. Cardiac markers, creatine phosphokinase and its MB fraction, and troponins I and T are typically markedly elevated.

Electrocardiogram

In CS due to acute MI with LV failure, Q waves and/or >2-mm ST elevation in multiple leads or left bundle branch block are usually present. More than one-half of all infarcts associated with shock are anterior. Global ischemia due to severe left main stenosis usually is accompanied by severe (e.g., >3 mm) ST depressions in multiple leads.

Chest roentgenogram

The chest x-ray typically shows pulmonary vascular congestion and often pulmonary edema, but these findings may be absent in up to a third of patients. The heart size is usually normal when CS results from a first MI but is enlarged when it occurs in a patient with a previous MI.

Echocardiogram

A two-dimensional echocardiogram with color-flow Doppler (**Chap. 12**) should be obtained promptly in

patients with suspected CS to help define its etiology. Doppler mapping demonstrates a left-to-right shunt in patients with VSR and the severity of MR when the latter is present. Proximal aortic dissection with aortic regurgitation or tamponade may be visualized, or evidence for pulmonary embolism may be obtained (**Chap. 45**).

Pulmonary artery catheterization

The use of pulmonary artery (Swan-Ganz) catheters in patients with established or suspected CS is controversial (**Chap. 13**). Their use is generally recommended for measurement of filling pressures and cardiac output to confirm the diagnosis and to optimize the use of IV fluids, inotropic agents, and vasopressors in persistent shock (**Table 34-2**). O₂ saturation measurement from right atrial, RV, and pulmonary arterial blood samples can rule out a left-to-right shunt. In CS, low mixed venous O₂ saturations and elevated arteriovenous (AV) O₂ differences reflect low cardiac index and high fractional O₂ extraction. However, when sepsis accompanies

TABLE 34-2 HEMODYNAMIC PATTERNS^a

	RA, MMHG	RVS, MMHG	RVD, MMHG	PAS, MMHG	PAD, MMHG	PCW, MMHG	CI, (L/MIN)/M ²	SVR, (DYN · S)/CM ⁵
Normal values	<6	<25	0–12	<25	0–12	<6–12	≥2.5	(800–1600)
MI without pulmonary edema ^b	–	–	–	–	–	~13 (5–18)	~2.7 (2.2–4.3)	–
Pulmonary edema	↔↑	↔↑	↔↑	↑	↑	↑	↔↓	↑
Cardiogenic shock								
LV failure	↔↑	↔↑	↔↑	↔↑	↑	↑	↓	↔↑
RV failure ^c	↑	↓↔↑ ^d	↑	↓↔↑ ^d	↔↓↑ ^d	↓↔↑ ^d	↓	↑
Cardiac tamponade	↑	↔↑	↑	↔↑	↔↑	↔↑	↓	↑
Acute mitral regurgitation	↔↑	↑	↔↑	↑	↑	↑	↔↓	↔↑
Ventricular septal rupture	↑	↔↑	↑	↔↑	↔↑	↔↑	↑PBF ↓SBF	↔↑
Hypovolemic shock	↓	↔↓	↔↓	↓	↓	↓	↓	↑
Septic shock	↓	↔↓	↔↓	↓	↓	↓	↑	↓

^aThere is significant patient-to-patient variation. Pressure may be normalized if cardiac output is low.

^bForrester et al classified nonreperfused MI patients into four hemodynamic subsets. (From JS Forrester et al: N Engl J Med 295:1356, 1976.) PCW pressure and CI in clinically stable subset 1 patients are shown. Values in parentheses represent range.

^c"Isolated" or predominant RV failure.

^dPCW and pulmonary artery pressures may rise in RV failure after volume loading due to RV dilation and right-to-left shift of the interventricular septum, resulting in impaired LV filling. When biventricular failure is present, the patterns are similar to those shown for LV failure.

Abbreviations: CI, cardiac index; MI, myocardial infarction; P/SBF, pulmonary/systemic blood flow; PAS/D, pulmonary artery systolic/diastolic; PCW, pulmonary capillary wedge; RA, right atrium; RVS/D, right ventricular systolic/diastolic; SVR, systemic vascular resistance.

Source: Table prepared with the assistance of Krishnan Ramanathan, MD.

CS, AV O₂ differences may not be elevated. The PCWP is elevated. Use of sympathomimetic amines may return these measurements and the systemic BP to normal. Systemic vascular resistance may be low, normal, or elevated in CS. Equalization of right- and left-sided filling pressures (right atrial and PCWP) suggests cardiac tamponade as the cause of CS (**Chap. 28**).

Left heart catheterization and coronary angiography

Measurement of LV pressure and definition of the coronary anatomy provide useful information and are indicated in most patients with CS complicating MI. Cardiac catheterization should be performed when there is a plan and capability for immediate coronary intervention (see below) or when a definitive diagnosis has not been made by other tests.

TREATMENT Acute Myocardial Infarction

GENERAL MEASURES (Fig. 34-2) In addition to the usual treatment of acute MI (**Chap. 41**), initial therapy is aimed at maintaining adequate systemic and coronary perfusion by raising systemic BP with vasopressors and adjusting volume status to a level that ensures optimum LV filling pressure. There is interpatient variability, but the values that generally are associated with adequate perfusion are systolic BP ~90 mmHg or mean BP >60 mmHg and PCWP >20 mmHg. Hypoxemia and acidosis must be corrected; most patients require ventilatory support (see “Pulmonary Edema,” below). Negative inotropic agents should be discontinued and the doses of renally cleared medications adjusted. Hyperglycemia should be controlled with insulin. Bradycardias may require transvenous pacing. Recurrent ventricular tachycardia or rapid atrial fibrillation may require immediate treatment (**Chap. 17**).

VASOPRESSORS Various IV drugs may be used to augment BP and cardiac output in patients with CS. All have important disadvantages, and none has been shown to change the outcome in patients with established shock. Norepinephrine is a potent vasoconstrictor and inotropic stimulant that is useful for patients with CS. As first line of therapy norepinephrine was associated with fewer adverse events, including arrhythmias, compared to a dopamine randomized trial of patients with several etiologies of circulatory shock. Although it did not significantly improve survival compared to dopamine, its relative safety suggests that norepinephrine is reasonable as initial vasopressor therapy. Norepinephrine should be started at a dose of 2 to 4 µg/min and titrated upward as necessary. If systemic perfusion or systolic pressure cannot be maintained at >90 mmHg with a dose of 15 µg/min, it is unlikely that a further increase will be beneficial.

Dopamine has varying hemodynamic effects based on the dose; at low doses (≤ 2 µg/kg per min), it dilates the renal

vascular bed, although its outcome benefits at this low dose have not been demonstrated conclusively; at moderate doses (2–10 µg/kg per min), it has positive chronotropic and inotropic effects as a consequence of β-adrenergic receptor stimulation. At higher doses, a vasoconstrictor effect results from α-receptor stimulation. It is started at an infusion rate of 2–5 µg/kg per min, and the dose is increased every 2–5 min to a maximum of 20–50 µg/kg per min. Dobutamine is a synthetic sympathomimetic amine with positive inotropic action and minimal positive chronotropic activity at low doses (2.5 µg/kg per min) but moderate chronotropic activity at higher doses. Although the usual dose is up to 10 µg/kg per min, its vasodilating activity precludes its use when a vasoconstrictor effect is required.

MECHANICAL CIRCULATORY SUPPORT Circulatory assist devices can be placed percutaneously or surgically and can be used to support the left, right, or both ventricles. Venoarterial extracorporeal membrane oxygenation (VA ECMO, a pump in combination with an oxygenator) may be used when respiratory failure accompanies biventricular failure. Temporary percutaneous devices can be used as a bridge to surgically implanted devices in community hospital settings or when neurologic status is uncertain. The most commonly used device is an intraaortic balloon pump (IABP), which is inserted into the aorta via the femoral artery and provides temporary hemodynamic support. However, routine IABP use in conjunction with early revascularization (predominantly with percutaneous coronary intervention [PCI]) did not reduce 30-day mortality in the IABP-SHOCK II trial. Although other percutaneous devices, including VA ECMO, result in better hemodynamic support compared to IABP, the effects on clinical outcomes are unknown. Surgically implanted devices can support the circulation as bridging therapy for cardiac transplant candidates or as destination therapy (**Chap. 21**). Assist devices should be used selectively in suitable patients in consultation with advanced heart failure specialists.

REPERFUSION-REVASCLARIZATION The rapid establishment of blood flow in the infarct-related artery is essential in the management of CS and forms the centerpiece of management. The randomized SHOCK Trial demonstrated that 132 lives were saved per 1000 patients treated with early revascularization with PCI or coronary artery bypass graft (CABG) compared with initial medical therapy including IABP with fibrinolytics followed by delayed revascularization. The benefit is seen across the risk strata and is sustained up to 11 years after an MI. Early revascularization with PCI or CABG is recommended in candidates suitable for aggressive care.

Prognosis

Within this high-risk condition, there is a wide range of expected death rates based on age, severity of hemodynamic abnormalities, severity of the clinical

manifestations of hypoperfusion, and the performance of early revascularization.

SHOCK SECONDARY TO RIGHT VENTRICULAR INFARCTION

Although transient hypotension is common in patients with RV infarction and inferior MI (**Chap. 41**), persistent CS due to RV failure accounts for only 3% of CS complicating MI. The salient features of RV shock are absence of pulmonary congestion, high right atrial pressure (which may be seen only after volume loading), RV dilation and dysfunction, only mildly or moderately depressed LV function, and predominance of single-vessel proximal right coronary artery occlusion. Management includes IV fluid administration to optimize right atrial pressure (10–15 mmHg); avoidance of excess fluids, which cause a shift of the interventricular septum into the LV; sympathomimetic amines; the early reestablishment of infarct-artery flow; and assist devices.

MITRAL REGURGITATION

Acute severe MR due to papillary muscle dysfunction and/or rupture may complicate MI and result in CS and/or pulmonary edema (see also **Chap. 41**). This complication most often occurs on the first day, with a second peak several days later. The diagnosis is confirmed by echo-Doppler. Rapid stabilization with IABP is recommended, with administration of dobutamine as needed to raise cardiac output. Reducing the load against which the LV pumps (afterload) reduces the volume of regurgitant flow of blood into the left atrium. Mitral valve surgery is the definitive therapy and should be performed early in the course in suitable candidates.

VENTRICULAR SEPTAL RUPTURE

Echo-Doppler demonstrates shunting of blood from the left to the right ventricle and may visualize the opening in the interventricular septum (see also **Chap. 41**). Timing and management are similar to those for MR with IABP support and surgical correction for suitable candidates.

FREE WALL RUPTURE

Myocardial rupture is a dramatic complication of STEMI that is most likely to occur during the first week after the onset of symptoms; its frequency increases with the age of the patient. The clinical presentation typically is a sudden loss of pulse, blood pressure, and consciousness but sinus rhythm on ECG (pulseless electrical activity) due to cardiac tamponade (**Chap. 28**). Free wall rupture may also result in CS due to subacute tamponade when the pericardium temporarily seals the rupture sites. Definitive surgical repair is required.

ACUTE FULMINANT MYOCARDITIS

Myocarditis can mimic acute MI with ST deviation or bundle branch block on the ECG and marked elevation of cardiac markers (see also **Chap. 27**). Acute myocarditis causes CS in a small proportion of cases. These patients are typically younger than those with CS due to acute MI and often do not have typical ischemic chest pain. Echocardiography usually shows global LV dysfunction. Initial management is the same as for CS complicating acute MI (Fig. 34-2) but does not involve coronary revascularization. Endomyocardial biopsy is recommended to determine the diagnosis and need for immunosuppressives for entities such as giant cell myocarditis. Refractory CS can be managed with assist devices with or without ECMO.

PULMONARY EDEMA

The etiologies and pathophysiology of pulmonary edema are discussed in **Chap. 5**.

Diagnosis

Acute pulmonary edema usually presents with the rapid onset of dyspnea at rest, tachypnea, tachycardia, and severe hypoxemia. Crackles and wheezing due to alveolar flooding and airway compression from peribronchial cuffing may be audible. Release of endogenous catecholamines often causes hypertension.

It is often difficult to distinguish between cardiogenic and noncardiogenic causes of acute pulmonary edema. Echocardiography may identify systolic and diastolic ventricular dysfunction and valvular lesions. Electrocardiographic ST elevation and evolving Q waves are usually diagnostic of acute MI and should prompt immediate institution of MI protocols and coronary artery reperfusion therapy (**Chap. 41**). Brain natriuretic peptide levels, when substantially elevated, support heart failure as the etiology of acute dyspnea with pulmonary edema (**Chap. 19**).

The use of a Swan-Ganz catheter permits measurement of PCWP and helps differentiate high-pressure (cardiogenic) from normal-pressure (noncardiogenic) causes of pulmonary edema. Pulmonary artery catheterization is indicated when the etiology of the pulmonary edema is uncertain, when edema is refractory to therapy, or when it is accompanied by hypotension. Data derived from use of a catheter often alter the treatment plan, but no impact on mortality rates has been demonstrated.

TREATMENT Pulmonary Edema

The treatment of pulmonary edema depends on the specific etiology. As an acute, life-threatening condition, a number of measures must be applied immediately to support

the circulation, gas exchange, and lung mechanics. Simultaneously, conditions that frequently complicate pulmonary edema, such as infection, acidemia, anemia, and acute kidney dysfunction, must be corrected.

SUPPORT OF OXYGENATION AND VENTILATION Patients with acute cardiogenic pulmonary edema generally have an identifiable cause of acute LV failure—such as arrhythmia, ischemia/infarction, or myocardial decompensation (**Chap. 19**)—that may be rapidly treated, with improvement in gas exchange. In contrast, noncardiogenic edema usually resolves much less quickly, and most patients require mechanical ventilation.

Oxygen Therapy Support of oxygenation is essential to ensure adequate O₂ delivery to peripheral tissues, including the heart.

Positive-Pressure Ventilation Pulmonary edema increases the work of breathing and the O₂ requirements of this work, imposing a significant physiologic stress on the heart. When oxygenation or ventilation is not adequate in spite of supplemental O₂, positive-pressure ventilation by face or nasal mask or by endotracheal intubation should be initiated. Noninvasive ventilation can rest the respiratory muscles, improve oxygenation and cardiac function, and reduce the need for intubation. In refractory cases, mechanical ventilation can relieve the work of breathing more completely than can noninvasive ventilation. Mechanical ventilation with positive end-expiratory pressure can have multiple beneficial effects on pulmonary edema: (1) decreases both preload and afterload, thereby improving cardiac function; (2) redistributes lung water from the intraalveolar to the extraalveolar space, where the fluid interferes less with gas exchange; and (3) increases lung volume to avoid atelectasis.

REDUCTION OF PRELOAD In most forms of pulmonary edema, the quantity of extravascular lung water is determined by both the PCWP and the intravascular volume status.

Diuretics The “loop diuretics” furosemide, bumetanide, and torsemide are effective in most forms of pulmonary edema, even in the presence of hypoalbuminemia, hyponatremia, or hypochloremia. Furosemide is also a venodilator that rapidly reduces preload before any diuresis, and is the diuretic of choice. The initial dose of furosemide should be ≤ 0.5 mg/kg, but a higher dose (1 mg/kg) is required in patients with renal insufficiency, chronic diuretic use, or hypervolemia or after failure of a lower dose.

Nitrates Nitroglycerin and isosorbide dinitrate act predominantly as venodilators but have coronary vasodilating properties as well. They are rapid in onset and effective when administered by a variety of routes. Sublingual nitroglycerin (0.4 mg $\times$ 3 every 5 min) is first-line therapy for acute cardiogenic pulmonary edema. If pulmonary edema persists in the absence of hypotension, sublingual may be followed by IV nitroglycerin, commencing at 5–10 μ g/min. IV nitroprusside (0.1–5 μ g/kg per min) is a potent venous and arterial vasodilator. It is useful for patients with pulmonary edema and hypertension but is

not recommended in states of reduced coronary artery perfusion. It requires close monitoring and titration using an arterial catheter for continuous BP measurement.

Morphine Given in 2- to 4-mg IV boluses, morphine is a transient venodilator that reduces preload while relieving dyspnea and anxiety. These effects can diminish stress, catecholamine levels, tachycardia, and ventricular afterload in patients with pulmonary edema and systemic hypertension.

Angiotensin-Converting Enzyme (ACE) Inhibitors ACE inhibitors reduce both afterload and preload and are recommended for hypertensive patients. A low dose of a short-acting agent may be initiated and followed by increasing oral doses. In acute MI with heart failure, ACE inhibitors reduce short- and long-term mortality rates.

Other Preload-Reducing Agents IV recombinant brain natriuretic peptide (nesiritide) is a potent vasodilator with diuretic properties and is effective in the treatment of cardiogenic pulmonary edema. It should be reserved for refractory patients and is not recommended in the setting of ischemia or MI.

Physical Methods In nonhypotensive patients, venous return can be reduced by use of the sitting position with the legs dangling along the side of the bed.

Inotropic and Inodilator Drugs The sympathomimetic amines dopamine and dobutamine (see above) are potent inotropic agents. The bipyridine phosphodiesterase-3 inhibitors (inodilators), such as milrinone (50 μ g/kg followed by 0.25–0.75 μ g/kg per min), stimulate myocardial contractility while promoting peripheral and pulmonary vasodilation. Such agents are indicated in patients with cardiogenic pulmonary edema and severe LV dysfunction.

Digitalis Glycosides Once a mainstay of treatment because of their positive inotropic action (**Chap. 19**), digitalis glycosides are rarely used at present. However, they may be useful for control of ventricular rate in patients with rapid atrial fibrillation or flutter and LV dysfunction, because they do not have the negative inotropic effects of other drugs that inhibit atrioventricular nodal conduction.

Intraaortic Balloon Counterpulsation IABP or other LV-assist devices (**Chap. 21**) may help relieve cardiogenic pulmonary edema and are indicated when refractory pulmonary edema results from the etiologies discussed in the CS section, especially in preparation for surgical repair.

Treatment of Tachyarrhythmias and Atrial-Ventricular Resynchronization (See also Chap. 18) Sinus tachycardia or atrial fibrillation can result from elevated left atrial pressure and sympathetic stimulation. Tachycardia itself can limit LV filling time and raise left atrial pressure further. Although relief of pulmonary congestion will slow the sinus rate or ventricular response in atrial fibrillation, a primary tachyarrhythmia may require cardioversion. In patients with reduced LV function and without atrial contraction or with lack of synchronized atrioventricular

contraction, placement of an atrioventricular sequential pacemaker should be considered (**Chap. 15**).

Stimulation of Alveolar Fluid Clearance A variety of drugs can stimulate alveolar epithelial ion transport and upregulate the clearance of alveolar solute and water, but this strategy has not been proven beneficial in clinical trials thus far.

SPECIAL CONSIDERATIONS

Risk of Iatrogenic Cardiogenic Shock In the treatment of pulmonary edema, vasodilators lower BP, and their use, particularly in combination, may lead to hypotension, coronary artery hypoperfusion, and shock (Fig. 34-1). In general, patients with a hypertensive response to pulmonary edema tolerate and benefit from these medications. In normotensive patients, low doses of single agents should be instituted sequentially, as needed.

Acute Coronary Syndromes (See also Chap. 41) Acute STEMI complicated by pulmonary edema is associated with in-hospital mortality rates of 20–40%. After immediate stabilization, coronary artery blood flow must be reestablished rapidly. When available, primary PCI is preferable; alternatively, a fibrinolytic agent should be administered. Early coronary angiography and revascularization by PCI or CABG also are indicated for patients with non-ST elevation acute coronary

syndrome. Assist devices may be used selectively as noted for refractory pulmonary edema.

Extracorporeal Membrane Oxygenation For patients with acute, severe noncardiogenic edema with a potential rapidly reversible cause, ECMO may be considered as a temporizing supportive measure to achieve adequate gas exchange. Usually venovenous ECMO is used in this setting.

Unusual Types of Edema Specific etiologies of pulmonary edema may require particular therapy. Reexpansion pulmonary edema can develop after removal of longstanding pleural space air or fluid. These patients may develop hypotension or oliguria resulting from rapid fluid shifts into the lung. Diuretics and preload reduction are contraindicated, and intravascular volume repletion often is needed while supporting oxygenation and gas exchange.

High-altitude pulmonary edema often can be prevented by use of dexamethasone, calcium channel-blocking drugs, or long-acting inhaled β_2 -adrenergic agonists. Treatment includes descent from altitude, bed rest, oxygen, and, if feasible, inhaled nitric oxide; nifedipine may also be effective.

For pulmonary edema resulting from upper airway obstruction, recognition of the obstructing cause is key, because treatment then is to relieve or bypass the obstruction.

CHAPTER 35

CARDIOVASCULAR COLLAPSE, CARDIAC ARREST, AND SUDDEN CARDIAC DEATH



Robert J. Myerburg ■ Agustin Castellanos

OVERVIEW AND DEFINITIONS

Sudden cardiac death (SCD) is defined as natural death due to cardiac causes in a person who may or may not have previously recognized heart disease but in whom the time and mode of death are unexpected. The term “sudden,” in the context of SCD, is defined for most clinical and epidemiologic purposes as 1 h or less between a change in clinical status heralding the onset of the terminal clinical event and the cardiac arrest itself. One exception is unwitnessed deaths, in which pathologists may expand the temporal definition to 24 h after the victim was last seen to be alive and stable.

Another exception is the variable interval between cardiac arrest and biological death that results from community-based interventions, following which

victims may remain biologically alive for days or even weeks after a cardiac arrest that has resulted in irreversible central nervous system damage. Confusion in terms can be avoided by adhering strictly to definitions of cardiovascular collapse, cardiac arrest, and death ([Table 35-1](#)). Although cardiac arrest is often potentially reversible by appropriate and timely interventions, death is biologically, legally, and literally an absolute and irreversible event. Biological death may be delayed by interventions, but the relevant pathophysiologic event remains the sudden and unexpected cardiac arrest. Accordingly, for statistical purposes, deaths that occur during hospitalization or within 30 days after resuscitated cardiac arrest are counted as sudden deaths.

TABLE 35-1

DISTINCTION BETWEEN CARDIOVASCULAR COLLAPSE, CARDIAC ARREST, AND DEATH			
TERM	DEFINITION	QUALIFIERS	MECHANISMS
Cardiovascular collapse	Sudden loss of effective blood flow due to cardiac and/or peripheral vascular factors that may reverse spontaneously (e.g., neurocardiogenic syncope, vasovagal syncope) or require interventions (e.g., cardiac arrest)	Nonspecific term: includes cardiac arrest and its consequences and transient events that characteristically revert spontaneously	Same as “Cardiac Arrest,” plus vasodepressor syncope or other causes of transient loss of blood flow
Cardiac arrest	Abrupt cessation of cardiac mechanical function, which may be reversible by a prompt intervention but will lead to death in its absence	Rare spontaneous reversions; likelihood of successful intervention relates to mechanism of arrest, clinical setting, and prompt return of circulation	Ventricular fibrillation, ventricular tachycardia, asystole, bradycardia, pulseless electrical activity, noncardiac mechanical factors (e.g., pulmonary embolism)
Sudden cardiac death	Sudden, irreversible cessation of all biological functions	None	

Source: Modified from RJ Myerburg, A Castellanos: Cardiac arrest and sudden cardiac death, in P Libby et al (eds): Braunwald's Heart Disease, 8th ed. Philadelphia, Saunders, 2008.

The majority of natural deaths are caused by cardiac disorders. However, it is common for underlying heart diseases—often far advanced—to go unrecognized before the fatal event. As a result, up to two-thirds of all SCDs occur as the first clinical expression of previously undiagnosed disease or in patients with known heart disease, the extent of which suggests low individual risk. The magnitude of sudden cardiac death as a public health problem is highlighted by the estimate that ~50% of all cardiac deaths are sudden and unexpected, accounting for a total SCD burden estimated to range from <200,000 to >450,000 deaths each year in the United States. SCD is a direct consequence of cardiac arrest, which may be reversible if addressed promptly. Because resuscitation techniques and emergency rescue systems are available to respond to victims of out-of-hospital cardiac arrest, which was uniformly fatal in the past, understanding the SCD problem has practical clinical importance.

CLINICAL DEFINITION OF FORMS OF CARDIOVASCULAR COLLAPSE

Cardiovascular collapse is a general term connoting loss of sufficient cerebral blood flow to maintain consciousness due to acute dysfunction of the heart and/or peripheral vasculature. It may be caused by vasodepressor syncope (vasovagal syncope, postural hypotension with syncope, neurocardiogenic syncope) a transient severe bradycardia, or cardiac arrest. The latter is distinguished from the transient forms of cardiovascular collapse in that it usually requires an active intervention to restore spontaneous blood flow. In contrast, vasodepressor syncope and other primary bradyarrhythmic syncopal events are transient and non-life-threatening, with spontaneous return of consciousness.

In the past, the most common electrical mechanism for cardiac arrest was ventricular fibrillation (VF) or pulseless sustained ventricular tachycardia (PVT). These were the initial rhythms recorded in 60–80% of cardiac arrests, with VF being the far more common of the two. Severe persistent bradyarrhythmias, asystole, and pulseless electrical activity (PEA; organized electrical activity, unusually slow, without mechanical response, formerly called electromechanical dissociation [EMD]) caused another 20–30%. Currently, asystole has emerged as the most common mechanism recorded at initial contact (45–50% of cases). PEA accounts for 20–25%, and VF is now present on initial contact in 25–35%. Undoubtedly, a significant proportion of the asystole cases began as VF and deteriorated to asystole because of long response times, but there are data suggesting an absolute reduction in VF as well. Acute low cardiac output states, having a precipitous onset, also may present clinically as a cardiac arrest. These hemodynamic causes include

massive acute pulmonary emboli, internal blood loss from a ruptured aortic aneurysm, intense anaphylaxis, and cardiac rupture with tamponade after myocardial infarction (MI).

ETIOLOGY, INITIATING EVENTS, AND CLINICAL EPIDEMIOLOGY

Clinical, epidemiologic, and pathologic studies have provided information on the underlying structural substrates in victims of SCD and identified subgroups at high risk for SCD. In addition, studies of clinical physiology have begun to identify transient functional factors that may convert a long-standing underlying structural abnormality from a stable to an unstable state, leading to the onset of cardiac arrest ([Table 35-2](#)).

Cardiac disorders constitute the most common causes of sudden natural death. After an initial peak incidence of sudden death between birth and 6 months of age (sudden infant death syndrome [SIDS]), the incidence of sudden death declines sharply and remains low through childhood and adolescence. Among adolescents and young adults, the incidence of SCD is approximately 1 per 100,000 population per year. The incidence begins to increase in adults over age 30 years, reaching a second peak in the age range of 45–75 years, when it approximates 1–2 per 1000 per year among the unselected adult population. Increasing age within this range is associated with increasing risk for sudden cardiac death ([Fig. 35-1A](#)). From 1 to 13 years of age, only one of five sudden natural deaths is due to cardiac causes. Between 14 and 21 years of age, the proportion increases to 30%, and it rises to 88% in the middle-aged and elderly.

Young and middle-aged men and women have different susceptibilities to SCD, but the sex differences decrease and ultimately disappear with advancing age. The difference in risk for SCD parallels the differences in age-related risks for other manifestations of coronary heart disease (CHD) between men and women. As the gender gap for manifestations of CHD closes in the sixth to eighth decades of life, the excess risk of SCD in males progressively narrows. Despite the lower incidence among younger women, coronary risk factors such as cigarette smoking, diabetes, hyperlipidemia, and hypertension are highly influential, and SCD remains an important clinical and epidemiologic problem. The incidence of SCD among the African-American population appears to be higher than it is among the white population; the reasons remain uncertain.

Genetic factors contribute to the risk of acquiring CHD, and a genetic basis for its expression as SCD is being explored. A genetic hypothesis for at least part of the SCD risk is supported by data suggesting a familial predisposition to SCD as a specific form of expression

TABLE 35-2
CARDIAC ARREST AND SUDDEN CARDIAC DEATH

Structural Substrates and Causes	
I. Coronary heart disease	
A. Coronary artery abnormalities	
1. Chronic atherosclerotic lesions	
2. Active lesions (plaque fissuring, platelet aggregation, acute thrombosis)	
3. Anomalous coronary artery anatomy	
B. Myocardial infarction	
1. Healed	
2. Acute	
II. Myocardial hypertrophy	
A. Secondary	
B. Hypertrophic cardiomyopathy	
1. Obstructive	
2. Nonobstructive	
III. Dilated cardiomyopathy—primary muscle disease	
IV. Inflammatory and infiltrative disorders	
A. Myocarditis	
B. Noninfectious inflammatory diseases	
C. Infiltrative diseases	
V. Valvular heart disease	
VI. Electrophysiologic abnormalities, structural	
A. Anomalous pathways in Wolf-Parkinson-White syndrome	
B. Conducting system disease	
VII. Inherited disorders associated with electrophysiologic abnormalities (congenital long QT syndromes, right ventricular dysplasia, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, etc.)	
Triggers for Expression of Cardiac Arrest	
I. Alterations of coronary blood flow	
A. Transient ischemia	
B. Reperfusion after ischemia	
II. Low cardiac output states	
A. Heart failure	
1. Chronic	
2. Acute decompensation	
B. Shock	
III. Systemic metabolic abnormalities	
A. Electrolyte imbalance (e.g., hypokalemia)	
B. Hypoxemia, acidosis	
IV. Neurologic disturbances	
A. Autonomic fluctuations: central, neural, humoral	
B. Receptor function	
V. Toxic responses	
A. Proarrhythmic drug effects	
B. Cardiac toxins (e.g., cocaine, digitalis intoxication)	
C. Drug interactions	

of CHD. A parental history of SCD as a first cardiac event increases the probability that an acute coronary event in the offspring will express similarly. In a number of less common syndromes, such as hypertrophic cardiomyopathy, congenital long QT interval syndromes, right ventricular dysplasia, and the syndrome of right bundle branch block and nonischemic ST-segment elevations (Brugada syndrome), and other more rare syndromes, there is a specific inherited risk of ventricular arrhythmias and SCD (**Chap. 18**).

The etiologic structural substrates and functional factors contributing to expression of the SCD syndrome are listed in Table 35-2. Worldwide, and especially in Western cultures, coronary atherosclerotic heart disease is the most common structural abnormality associated with SCD in middle-aged and older adults. Up to 80% of all SCDs in the United States are due to the consequences of coronary atherosclerosis. The non-ischemic cardiomyopathies (dilated and hypertrophic, collectively; **Chap. 27**) account for another 10–15% of SCDs, and all the remaining diverse etiologies cause only 5–10% of all SCDs. The inherited arrhythmia syndromes (see above and Table 35-2) are proportionally more common causes in adolescents and young adults. For some of these syndromes, such as hypertrophic cardiomyopathy (**Chap. 27**), the risk of SCD increases significantly after the onset of puberty.

Transient ischemia in a previously scarred or hypertrophied heart, hemodynamic and fluid and electrolyte disturbances, fluctuations in autonomic nervous system activity, and transient electrophysiologic changes caused by drugs or other chemicals (e.g., proarrhythmia) have all been implicated as mechanisms responsible for the transition from electrophysiologic stability to instability. In addition, reperfusion of ischemic myocardium may cause transient electrophysiologic instability and arrhythmias.

PATHOLOGY

Data from postmortem examinations of SCD victims parallel the clinical observations on the prevalence of CHD as the major structural etiologic factor. More than 80% of SCD victims have pathologic findings of CHD. The pathologic description often includes a combination of long-standing, extensive atherosclerosis of the epicardial coronary arteries and unstable coronary artery lesions, which include various permutations of eroded, fissured, or ruptured plaques; platelet aggregates; hemorrhage; and/or thrombosis. As many as 70–75% of males who die suddenly have preexisting healed MIs, whereas only 20–30% have recent acute MIs, despite the prevalence of unstable plaques and thrombi. The latter suggests transient ischemia as the mechanism of onset. Regional or global left ventricular (LV) hypertrophy often coexists with prior MIs.

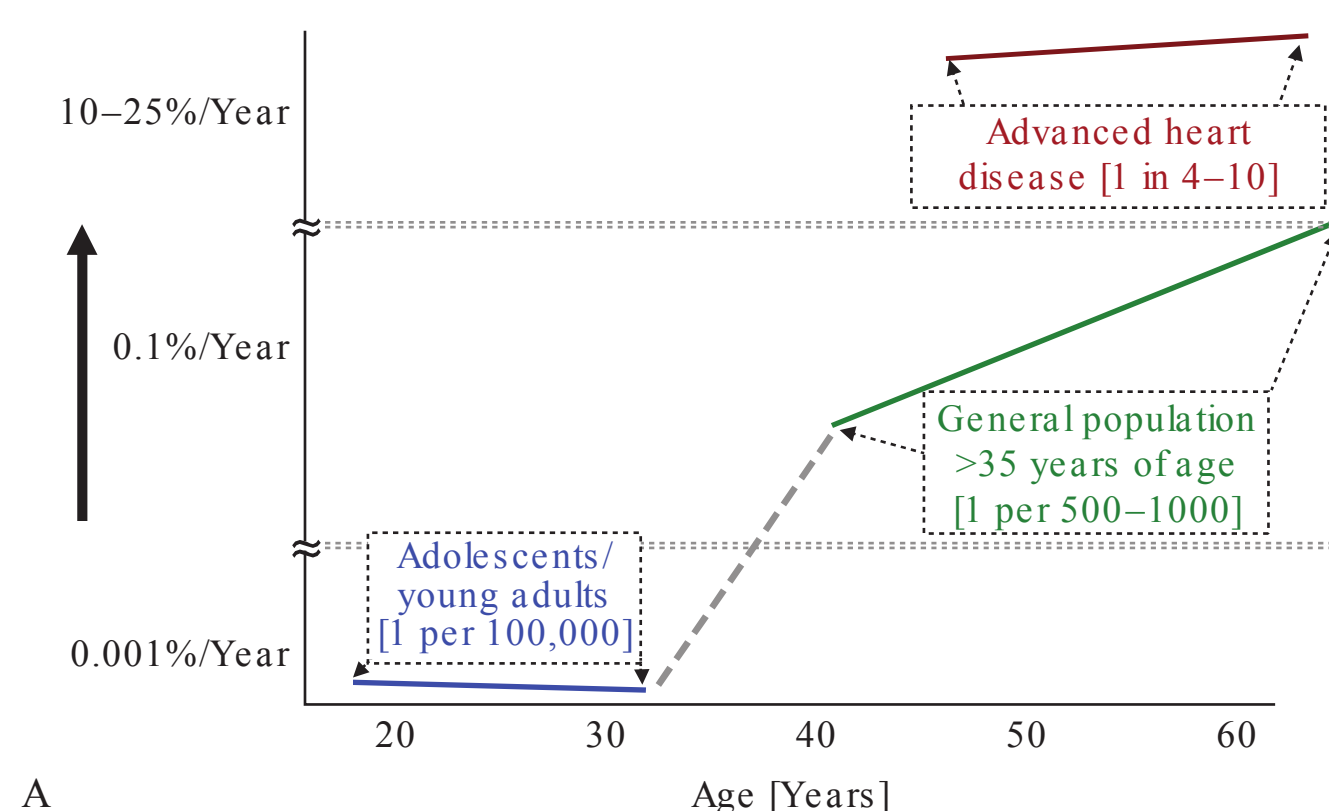
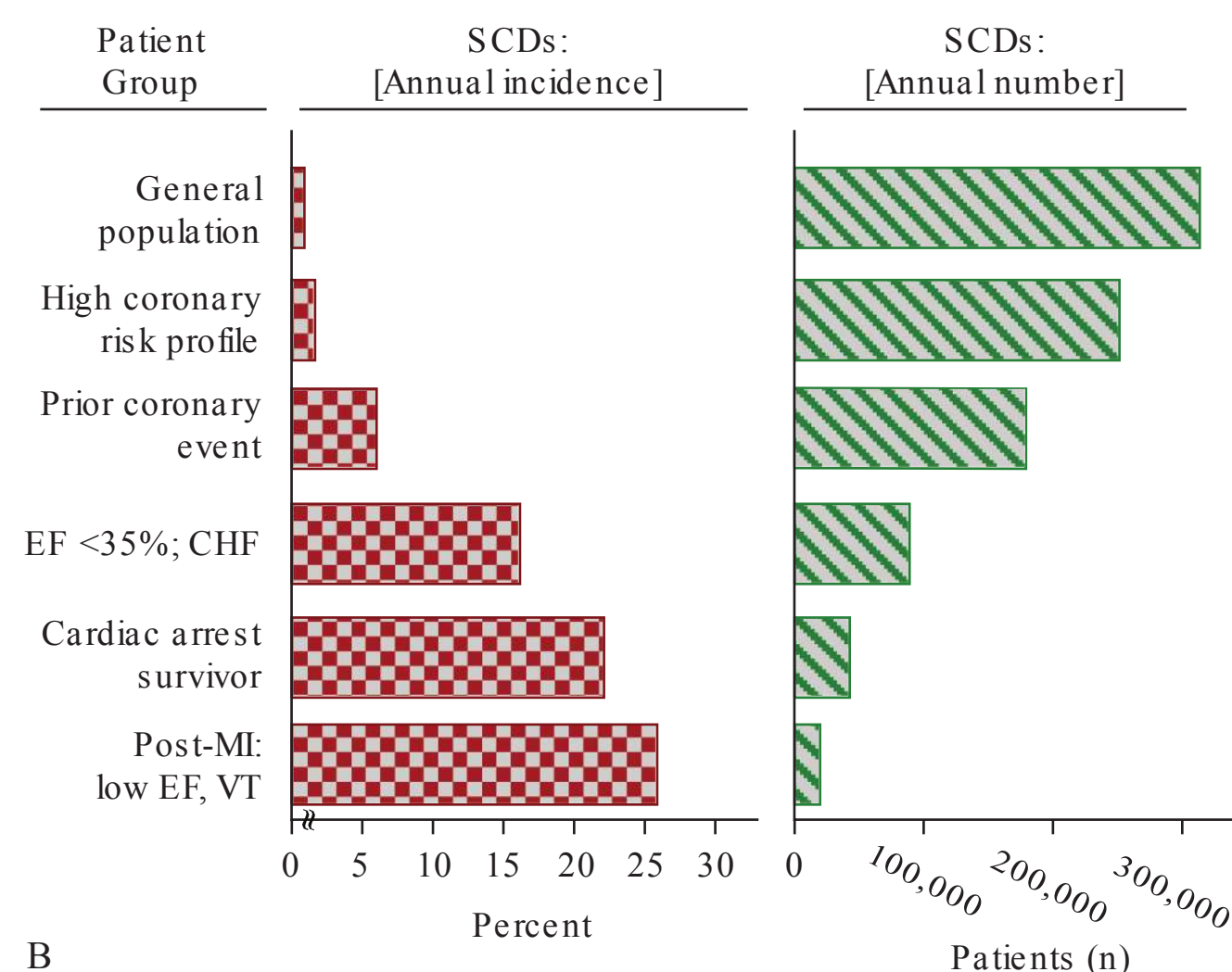


FIGURE 35-1

Panel A demonstrates age-related risk for sudden cardiac death (SCD). For the general population age 35 years and older, SCD risk is 0.1–0.2% per year (1 per 500–1000 population). Among the general population of adolescents and adults younger than age 30 years, the overall risk of SCD is 1 per 100,000 population, or 0.001% per year. The risk of SCD increases dramatically beyond age 35 years. The greatest rate of increase is between 40 and 65 years (vertical axis is discontinuous). Among patients older than 30 years of age, with advanced structural heart disease and markers of high risk for cardiac arrest, the event rate may exceed 25% per year, and age-related risk attenuates. (Modified from RJ Myerburg, A Castellanos: Cardiac arrest and sudden cardiac death, in P Libby et al [eds]: Braunwald's Heart Disease, 8th ed. Philadelphia, Saunders, 2008.) Panel B demonstrates the incidence of SCD in population subgroups and the relation of total number of events per year to incidence figures. Approximations of subgroup



incidence figures and the related population pool from which they are derived are presented. Approximately 50% of all cardiac deaths are sudden and unexpected. The incidence bars on the left (percent/year) indicate the approximate percentage of sudden and nonsudden deaths in each of the population subgroups indicated, ranging from the lowest percentage in unselected adult populations (0.1–2% per year) to the highest percentage in patients with severe left ventricular dysfunction and heart failure (approximately 25% per year). The bars on the right indicate the total number of events per year in each of these groups with the population impact size of each of the subgroups. The highest risk categories identify the smallest number of total annual events, and the lowest incidence category accounts for the largest number of events per year. CHF, congestive heart failure; EF, ejection fraction; MI, myocardial infarction; VT, ventricular tachycardia. (After RJ Myerburg et al: Circulation 85:2, 1992.)

PREDICTION AND PREVENTION OF CARDIAC ARREST AND SUDDEN CARDIAC DEATH

SCD accounts for approximately one-half the total number of cardiovascular deaths. As shown in Fig. 35-1B, the very-high-risk subgroups consist of more focused populations at higher risk of cardiac arrest or SCD, with better individual prediction, but the representation of such subgroups within the overall population burden of SCD is small. This is indicated by the absolute number of events (“events per year”), in contrast to the percentage per year in the subgroup. To achieve a major population impact, effective prevention of underlying diseases and the development of new epidemiologic and clinical probes that will allow better individual risk prediction by identifying specific high-risk subgroups within the large general populations are needed.

Strategies for predicting and preventing SCD are classified as primary and secondary. Primary prevention

refers to the attempt to identify individual patients at specific risk for SCD and institute preventive strategies. Secondary prevention refers to measures taken to prevent recurrent cardiac arrest or death in individuals who have survived a prior cardiac arrest.

The effectiveness of the prevention strategies currently used depends on the magnitude of risk among the various population subgroups. Because the annual incidence of SCD among the unselected adult population is limited to approximately 1 per 1000 population per year (Fig. 35-1) and ~50% of all SCDs due to coronary artery disease occur as the first clinical manifestation of the disease (Fig. 35-2A), the only currently practical strategies are profiling for risk of developing CHD and risk factor control (Fig. 35-2B). The most powerful long-term risk factors include age, cigarette smoking, elevated serum cholesterol, diabetes mellitus, elevated blood pressure, LV hypertrophy, and nonspecific electrocardiographic abnormalities. Markers of inflammation (e.g., levels of C-reactive protein) that may predict

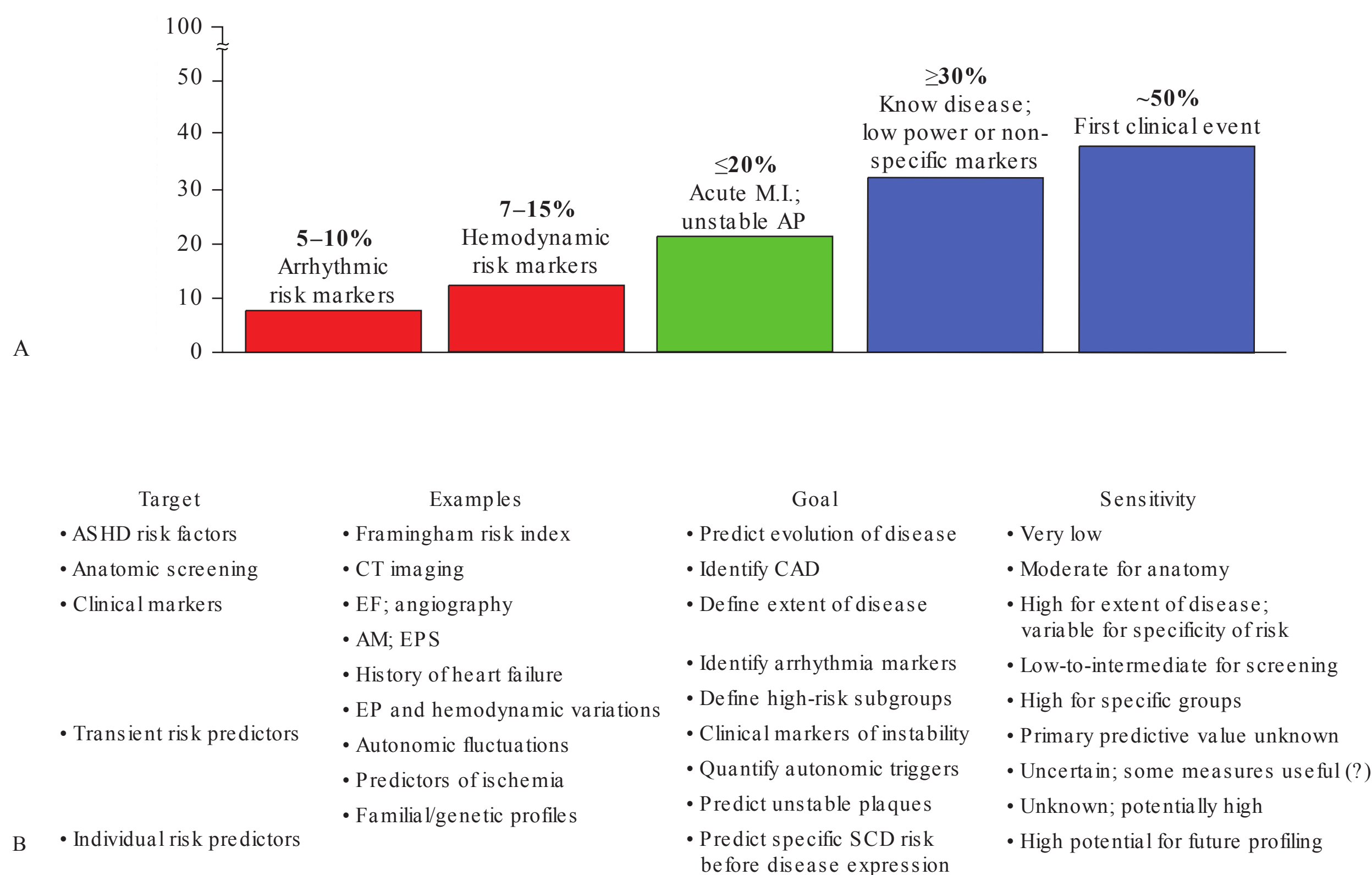


FIGURE 35-2
Population subsets, risk predictors, and distribution of sudden cardiac deaths (SCDs) according to clinical circumstances. A. The population subset with high-risk arrhythmia markers in conjunction with low ejection fraction is a group at high risk of SCD but accounts for <10% of the total SCD burden attributable to coronary artery disease. In contrast, 50% of all SCD victims present with SCD as the first and only manifestation of underlying disease, and up to 30% have known disease but are considered relatively low risk because of the absence of high-risk markers. B. Profiling for individual prediction and prevention of SCD is difficult. The highest absolute numbers of events occur among the

general population who may have risk factors for coronary heart disease or expressions of disease that do not predict high risk. This results in a low sensitivity for predicting and preventing SCD. New approaches that include epidemiologic modeling of transient risk factors and genetic predictors of individual patient risk offer hope for greater sensitivity in the future. AM, ambulatory monitoring; AP, angina pectoris; ASHD, arteriosclerotic heart disease; CAD, coronary artery disease; CT, computed tomography; EF, ejection fraction; EP, electrophysiologic; EPS, electrophysiologic study; MI, myocardial infarction. (Modified from RJ Myerburg: J Cardiovasc Electrophysiol 12:369–381, 2001.)

plaque destabilization have been added to risk classifications. The presence of multiple risk factors progressively increases incidence, but not sufficiently or specifically enough to warrant therapies targeted to potentially fatal arrhythmias (Fig. 35-1A). However, recent studies suggesting familial clustering of SCD associated with a first acute coronary syndrome offer hope that genetic markers for specific risk may be forthcoming.

After coronary artery disease has been identified in a patient, additional strategies for risk profiling become available (Fig. 35-2B), but the majority of SCDs occur among the large unselected groups rather than in the specific high-risk subgroups that become evident among populations with established disease (compare events per year with percentage per year in Fig. 35-1B). After a major cardiovascular event, such as acute MI, recent onset of heart failure, or survival after

out-of-hospital cardiac arrest, the highest risk of death occurs during the initial 6–18 months after the event and then plateaus toward the baseline risk associated with the extent of underlying disease. However, many of the early deaths are nonsudden, diluting the potential benefit of strategies targeted specifically to SCD. Thus, although post-MI beta blocker therapy has an identifiable benefit for both early SCD and nonsudden mortality risk, a total mortality benefit for implantable cardioverter-defibrillator (ICD) therapy early after MI has not been observed.

Among patients in the acute, convalescent, and chronic phases of MI (**Chap. 41**), subgroups at high absolute risk of SCD can be identified. During the acute phase, the potential risk of cardiac arrest from onset through the first 48 h used to be as high as 15%, but is now reported in the range of 2.3–4.4% because of early patient awareness

of the significance of symptoms and the availability of emergency revascularization strategies. Those who survive acute-phase VF are not at continuing risk for recurrent cardiac arrest indexed to that event. During the convalescent phase after MI (3 days to ~6 weeks), an episode of sustained ventricular tachycardia (VT) or VF, which is usually associated with a large infarct, predicts a natural history mortality risk of >25% at 12 months. At least one-half of the deaths are sudden. Aggressive intervention techniques may reduce this incidence.

During the chronic phase after MI, the longer-term risk for total mortality and SCD mortality is predicted by a number of factors (Fig. 35-2B). The most important for both SCD and nonsudden death is the extent of myocardial damage sustained as a result of the acute MI. This is measured by the magnitude of reduction of the ejection fraction (EF) and/or the occurrence of heart failure. Various studies have demonstrated that ventricular arrhythmias identified by ambulatory monitoring contribute significantly to this risk, especially in patients with an EF <40%. In addition, inducibility of VT or VF during electrophysiologic testing of patients who have ambient ventricular arrhythmias (premature ventricular contractions [PVCs] and nonsustained VT) and an EF <35% is a strong predictor of SCD risk. Patients in this subgroup are now considered candidates for ICDs (see below). Risk falls sharply with EFs >35% and the absence of ambient arrhythmias after MI, and conversely is high with EFs <30% even without the ambient arrhythmia markers.

The cardiomyopathies (dilated and hypertrophic, **Chap. 27**) are the second most common category of diseases associated with risk of SCD (Table 35-2). Some risk factors have been identified, largely related to extent of disease, presence of heart failure, documented ventricular arrhythmias, and syncope thought to be due to arrhythmias. The less common causes of SCD include valvular heart disease (primarily aortic) and inflammatory and infiltrative disorders of the myocardium. The latter include viral myocarditis, sarcoidosis, and amyloidosis.

Among adolescents and young adults, rare inherited disorders such as hypertrophic cardiomyopathy, the long QT interval syndromes, right ventricular dysplasia, and the Brugada syndrome have received attention as important causes of SCD, as has acute myocarditis and other less common acquired diseases. Among the subgroup of young competitive athletes, the incidence of SCD may be higher than it is for the general adolescent and young adult population, perhaps up to 1 in 75,000–100,000. Hypertrophic cardiomyopathy (**Chap. 27**) is the most common cause in the United States.

Secondary prevention strategies should be applied to survivors of cardiac arrest that was not associated with an acute MI or other controllable transient risk factors, such as certain drug exposures and correctable electrolyte imbalances. Multivessel coronary artery disease

and dilated cardiomyopathy, especially with markedly reduced left ventricular EF, predict a high risk of recurrence of cardiac arrest or SCD and are indications for specific interventions, such as ICDs (see below). The occurrence of otherwise unexplained syncope or documented life-threatening arrhythmias in patients with long QT syndromes or right ventricular dysplasia are also associated with increased risk of SCD.

CLINICAL CHARACTERISTICS OF CARDIAC ARREST

PRODROME, ONSET, ARREST, DEATH

SCD may be presaged by days to months of increasing angina, dyspnea, palpitations, easy fatigability, and other nonspecific complaints. However, these prodromal symptoms are generally predictive of any major cardiac event; they are not specific for predicting SCD.

The onset of the clinical transition, leading to cardiac arrest, is defined as an acute change in cardiovascular status preceding cardiac arrest by up to 1 h. When the onset is instantaneous or abrupt, the probability that the arrest is cardiac in origin is >95%. Continuous electrocardiogram (ECG) recordings fortuitously obtained at the onset of a cardiac arrest commonly demonstrate a tendency for the heart rate to increase and for advanced grades of PVCs to evolve during the minutes or hours before the event.

The probability of achieving successful resuscitation from cardiac arrest is related to the interval from onset of loss of circulation to return of spontaneous circulation (ROSC), the setting in which the event occurs, the mechanism (VF, VT, PEA, asystole), and the clinical status of the patient before the cardiac arrest. ROSC and survival rates as a result of defibrillation decrease almost linearly from the first minute to 10 min. After 4–5 min, survival rates are no better than 25–30% in out-of-hospital settings without bystander cardiopulmonary resuscitation (CPR). Those settings in which it is possible to institute prompt CPR followed by prompt defibrillation provide a better chance of a successful outcome. The outcome in intensive care units and other in-hospital environments is heavily influenced by the patient's preceding clinical status. The immediate outcome is good for cardiac arrest occurring in the intensive care unit in the presence of an acute cardiac event or transient metabolic disturbance, but survival among patients with far-advanced chronic cardiac disease or advanced noncardiac diseases (e.g., renal failure, pneumonia, sepsis, diabetes, cancer) is low and not much better in the in-hospital setting. Survival rates after unexpected cardiac arrest in unmonitored areas in a hospital do not differ from witnessed out-of-hospital arrests. Since implementation of community response systems, survival from out-of-hospital cardiac arrest has

improved, although it still remains low, under most circumstances. Survival probabilities in public sites exceed those in the home environment, where the majority of cardiac arrests occur.

The success rate for initial resuscitation and survival to hospital discharge after an out-of-hospital cardiac arrest depends heavily on the mechanism of the event. When the mechanism is pulseless VT, the outcome is best; VF is the next most successful; and asystole and PEA, now the most common mechanisms, generate dismal outcome statistics. Advanced age also adversely influences the chances of successful resuscitation.

The probability of progression to biologic death is a function of the mechanism of cardiac arrest and the length of the delay before interventions. VF without CPR within the first 4–6 min has a poor outcome even if defibrillation is successful because of secondary brain damage; the prompt interposition of bystander CPR (basic life support; see below) improves outcome at any point along the time scale, especially when followed by early successful defibrillation. However, there are few survivors among patients who had no life support activities for the first 8 min after onset. Evaluations of deployment of automatic external defibrillators (AEDs) in communities (e.g., police vehicles, large buildings, airports, and stadiums) are beginning to generate encouraging data, but the data for home deployment has been less impressive.

Death during the hospitalization after a successfully resuscitated cardiac arrest relates closely to the severity of central nervous system injury. Anoxic encephalopathy and infections subsequent to prolonged respirator dependence account for 60% of the deaths. Another 30% occur as a consequence of low cardiac output states that fail to respond to interventions. Recurrent arrhythmias are the least common cause of death, accounting for only 10% of in-hospital deaths.

In the setting of acute MI (**Chap. 41**), it is important to distinguish between primary and secondary cardiac arrests. Primary cardiac arrests are those that occur in the absence of hemodynamic instability, and secondary cardiac arrests are those that occur in patients in whom abnormal hemodynamics dominate the clinical picture before cardiac arrest. The success rate for immediate resuscitation in primary cardiac arrest during acute MI in a monitored setting should exceed 90%. In contrast, as many as 70% of patients with secondary cardiac arrest succumb immediately or during the same hospitalization.

TREATMENT Cardiac Arrest

An individual who collapses suddenly is managed in five stages: (1) initial evaluation and basic life support if cardiac arrest is confirmed, (2) public access defibrillation (when

available), (3) advanced life support, (4) postresuscitation care, and (5) long-term management. The initial response, including confirmation of loss of circulation, followed by basic life support and public access defibrillation, can be carried out by physicians, nurses, paramedical personnel, and trained laypersons.

INITIAL EVALUATION AND BASIC LIFE SUPPORT Confirmation that a sudden collapse with loss of consciousness (LOC) is due to a cardiac arrest includes prompt observations of the state of consciousness, respiratory movements, skin color, and the presence or absence of pulses in the carotid or femoral arteries. For lay responders, the pulse check is no longer recommended because it is unreliable. As soon as a cardiac arrest is suspected, confirmed, or even considered to be impending, calling an emergency rescue system (e.g., 911) is the immediate priority. With the development of AEDs that are easily used by nonconventional emergency responders, an additional layer for response has evolved (see below).

Careful attention to the respiratory status after abrupt LOC is important. Although normal breathing or tachypnea after LOC makes cardiac arrest less likely, gasping respiratory movements may persist during a true cardiac arrest, and their presence should not deter appropriate responses. In fact, continued gasping is considered a good prognostic sign for successful outcome. It is also important to observe for severe stridor with a persistent pulse as a clue to aspiration of a foreign body or food. If this is suspected, a Heimlich maneuver (see below) may dislodge the obstructing body. A precordial blow, or “thump,” delivered firmly with a clenched fist to the junction of the middle and lower thirds of the sternum may occasionally revert VT or VF, but there is concern about converting VT to VF. Therefore, it is recommended to use precordial thumps as a life support technique only when monitoring and defibrillation are available. This conservative application of the technique remains controversial.

The third action during the initial response is to clear the airway. The head is tilted back and the chin lifted so that the oropharynx can be explored to clear the airway. Dentures or foreign bodies are removed, and the Heimlich maneuver is performed if there is reason to suspect that a foreign body is lodged in the oropharynx. If respiratory arrest precipitating cardiac arrest is suspected, a second precordial thump is delivered after the airway is cleared.

Basic life support, more popularly known as CPR, is intended to maintain organ perfusion until definitive interventions can be instituted. The initial and primary element of CPR is maintenance of perfusion until spontaneous circulation can be restored. Closed chest cardiac compression maintains a pump function by sequential filling and emptying of the chambers, with competent valves maintaining forward direction of flow. The palm of one hand is placed over the lower sternum, with the heel of the other resting on the dorsum of the lower hand. The sternum is depressed, with the arms remaining straight, at a rate of 100 per minute. Sufficient force is applied to depress the sternum 4–5 cm, and relaxation is abrupt.

Until recently, providing ventilation of the lungs by mouth-to-mouth respiration was used if no specific rescue equipment was immediately available (e.g., plastic oropharyngeal airways, esophageal obturators, masked Ambu bag). However, ventilatory support during CPR has yielded to evidence that continuous chest compressions (“hands only” CPR) results in better outcomes. Compressions are interrupted only for single shocks from an AED when available, with 2 min of CPR between each single shock.

AUTOMATED EXTERNAL DEFIBRILLATION (AED) AEDs that are easily used by nonconventional responders, such as nonparamedic firefighters, police officers, ambulance drivers, trained security guards, and minimally trained or untrained laypersons, have been developed. This advance has inserted another level of response into the cardiac arrest paradigm. A number of studies have demonstrated that AED use by nonconventional responders in strategic response systems and public access lay responders can improve cardiac arrest survival rates. The rapidity with which defibrillation/cardioversion is achieved is an important element for successful resuscitation, both for ROSC and for protection of the central nervous system. Chest compressions should be carried out while the defibrillator is being charged. As soon as a diagnosis of VF or VT is established, a biphasic waveform shock of 150–200 J (360 J if a monophasic waveform device is used) should be delivered. If 5 min has elapsed between collapse and first contact with the victim, there is some evidence that 60–90 s of CPR before the first shock may improve probability of survival without neurologic damage. If the initial shock does not successfully revert VT or VF, chest compression at a rate of 100 per minute is resumed for 2 min, and then a second shock is delivered. Multiple shocks given in sequence are no longer recommended, in order to minimize interruptions of chest compressions. This sequence is continued until personnel capable of, and equipped for, advanced life support are available, although not much data support the notion that shocks and chest compressions alone will revert VF after three shocks have failed.

ADVANCED CARDIAC LIFE SUPPORT (ACLS) ACLS is intended to achieve and maintain organ perfusion and adequate ventilation, control cardiac arrhythmias, and stabilize blood pressure and cardiac output. The activities carried out to achieve these goals include (1) defibrillation/cardioversion and/or pacing, (2) intubation with an endotracheal tube, and (3) insertion of an intravenous line.

As in basic life support, the major emphasis during ACLS is minimizing interruptions of chest compressions until ROSC is achieved. After two or three unsuccessful defibrillation attempts, epinephrine, 1 mg IV, is given and attempts to defibrillate are repeated. The dose of epinephrine may be repeated after intervals of 3–5 min (**Fig. 35-3A**). Vasopressin (a single 40-unit dose given IV) has been suggested as an alternative to epinephrine.

If the patient is less than fully conscious upon reversion or if two or three attempts fail, prompt intubation, ventilation,

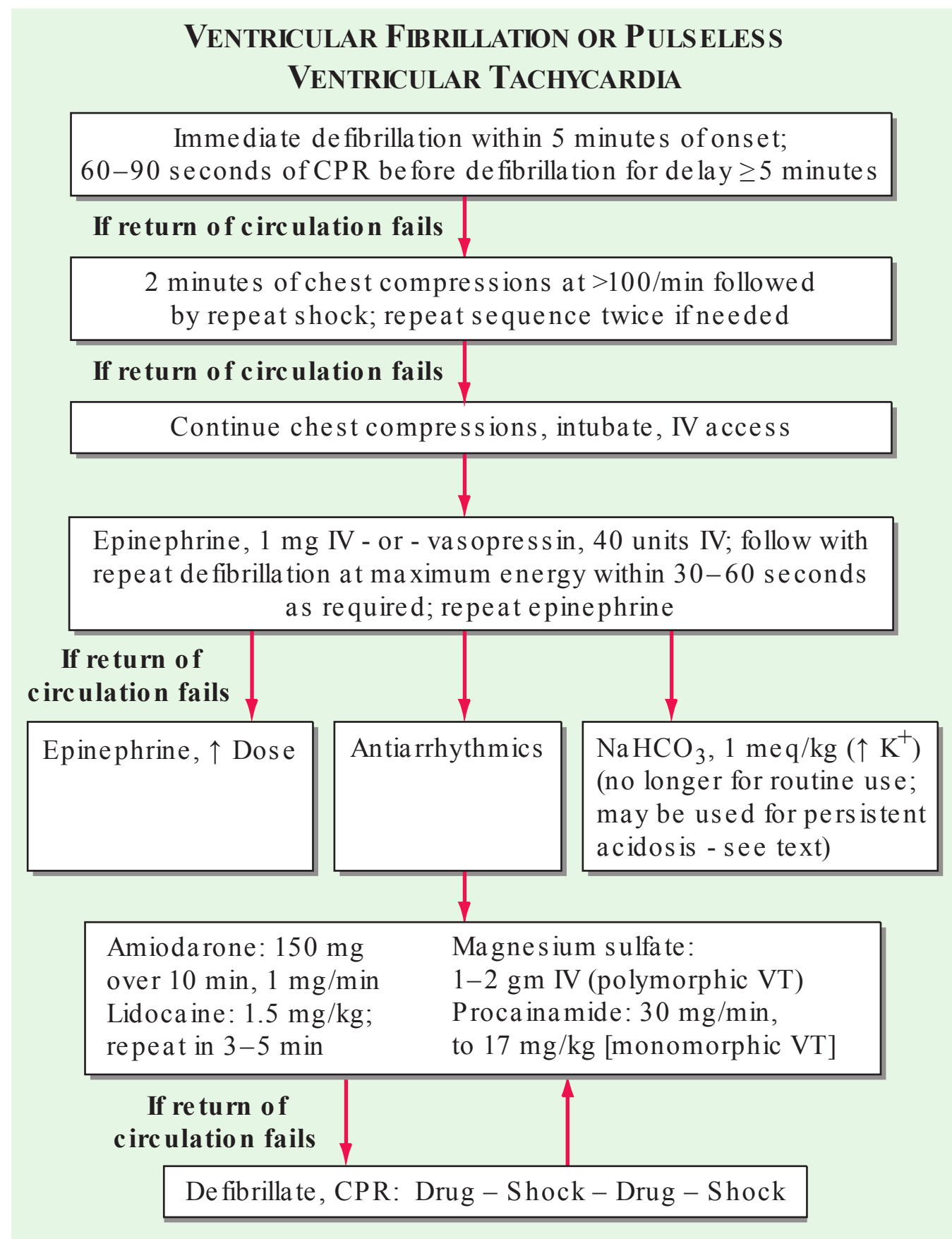
and arterial blood gas analysis should be carried out. Ventilation with O₂ (room air if O₂ is not immediately available) may promptly reverse hypoxemia and acidosis. Quantitative waveform capnography is now recommended for confirmation and monitoring of endotracheal tube placement. A patient who is persistently acidotic after successful defibrillation and intubation or had acidosis prior to arrest, may be given 1 meq/kg NaHCO₃ initially and an additional 50% of the dose repeated every 10–15 min. However, it should not be used routinely.

After initial unsuccessful defibrillation attempts or with persistent/recurrent electrical instability, antiarrhythmic therapy should be instituted. Intravenous amiodarone has emerged as the initial treatment of choice (150 mg over 10 min, followed by 1 mg/min for up to 6 h and 0.5 mg/min thereafter) (**Fig. 35-3A**). For cardiac arrest due to VF in the early phase of an acute coronary syndrome, a bolus of 1 mg/kg of lidocaine may be given intravenously as an alternative, and the dose may be repeated in 2 min. It also may be tried in patients in whom amiodarone is unsuccessful. Intravenous procainamide (loading infusion of 100 mg/5 min to a total dose of 500–800 mg, followed by continuous infusion at 2–5 mg/min) is now rarely used in this setting but may be tried for persisting, hemodynamically stable arrhythmias. Intravenous calcium gluconate is no longer considered safe or necessary for routine administration. It is used only in patients in whom acute hyperkalemia is known to be the triggering event for resistant VF, in the presence of known hypocalcemia, or in patients who have received toxic doses of calcium channel antagonists.

Cardiac arrest due to bradyarrhythmias or asystole (B/A cardiac arrest) is managed differently (**Fig. 35-3B**). The patient is promptly intubated, CPR is continued, and an attempt is made to control hypoxemia and acidosis and identify other reversible causes. Epinephrine may be given intravenously or by an intraosseous route. Atropine is no longer considered effective for asystole or PEA, but can be used for bradyarrhythmias. External pacing devices are used to attempt to establish a regular rhythm when atropine fails for a bradyarrhythmia, but chronotropic agents given intravenously are now recognized as an equally effective alternative.

The success rate may be good when B/A arrest is due to acute inferior wall MI or to correctable airway obstruction or drug-induced respiratory depression or with prompt resuscitation efforts. For acute airway obstruction, prompt removal of foreign bodies by the Heimlich maneuver or, in hospitalized patients, by intubation and suctioning of obstructing secretions in the airway is often successful. The prognosis is generally very poor in other causes of this form of cardiac arrest, such as end-stage cardiac or noncardiac diseases. Treatment of PEA is similar to that for bradyarrhythmias, but its outcome is also dismal.

POST-CARDIAC ARREST SYNDROME AND POSTRESUSCITATION CARE After return of spontaneous or stable assisted circulation, attention shifts to the diagnostic and therapeutic elements of the post-cardiac arrest syndrome. This recently developed clinical classification emerged from the



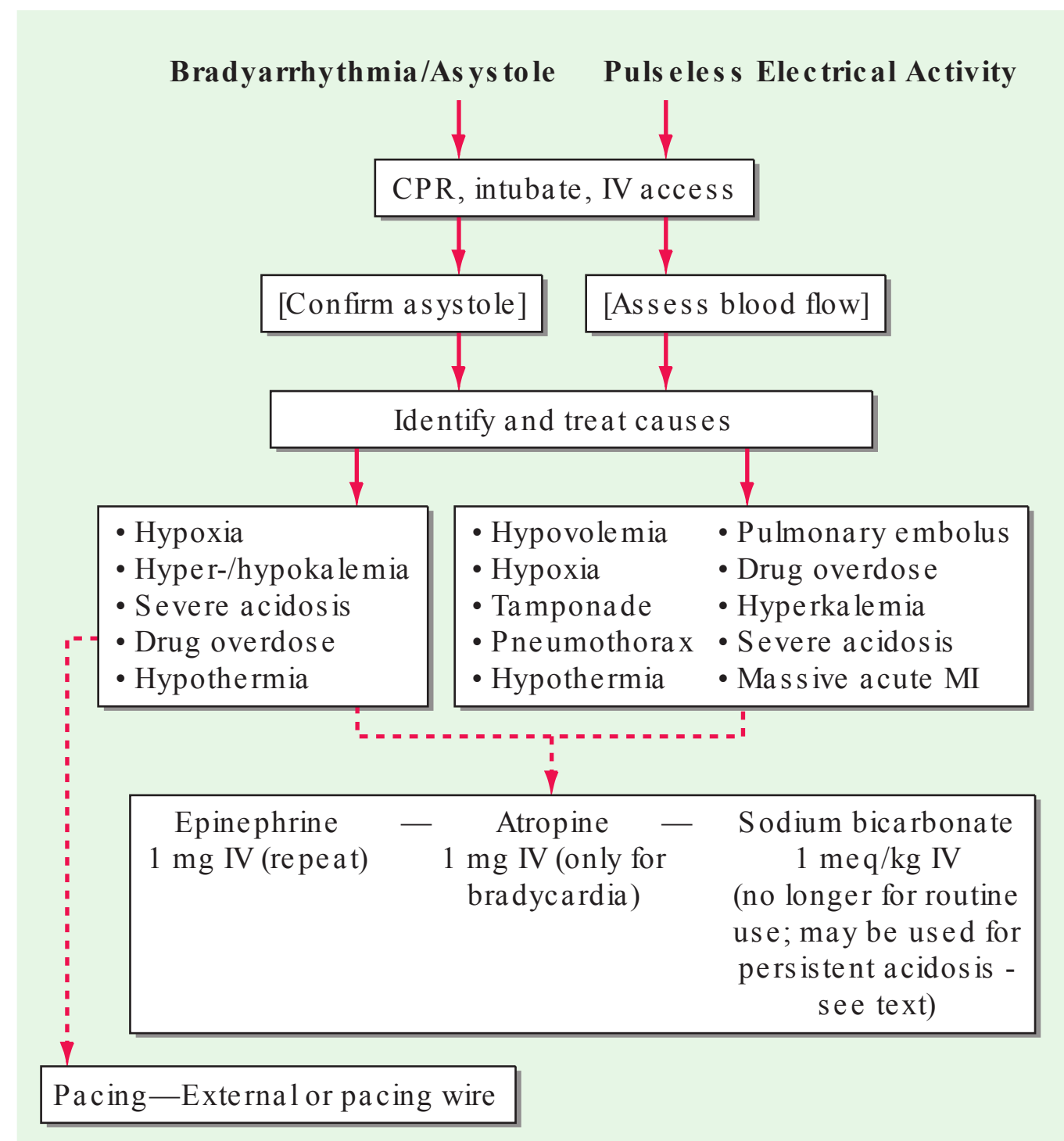
A

FIGURE 35-3

A. The algorithm of ventricular fibrillation or pulseless ventricular tachycardia begins with an initial defibrillation attempt. If a single shock fails to restore a pulse, it is followed by 2 min of cardiopulmonary resuscitation (CPR; chest compressions), followed by another single shock. After three such sequences, epinephrine and then antiarrhythmic drugs are added to the protocol. See

organization of the elements of injury following cardiac arrest into a multidisciplinary continuum. The four components of post-cardiac arrest syndrome include brain injury, myocardial dysfunction, systemic ischemia/reperfusion responses, and control of persistent precipitating factors. The therapeutic goal is to maintain a stable electrical, hemodynamic, and central nervous system status.

Postresuscitation care is determined by the specific clinical circumstances. The most pressing is the presence of anoxic encephalopathy, which is a strong predictor of in-hospital death and postarrest disability. Mild therapeutic hypothermia is indicated for resuscitated cardiac arrest victims who are hemodynamically stable, but remain comatose. Core body temperature is decreased to 32–34°C, by several available techniques (external and/or internal [core]), as soon as practical after resuscitation and maintained for a minimum of 12–24 h. By reducing metabolic demands and cerebral edema, this intervention improves probability of survival with better neurologic outcome.



B

text for details. B. The algorithms for bradyarrhythmia/asystole (left) or pulseless electrical activity (right) are dominated first by continued life support and a search for reversible causes. Subsequent therapy is nonspecific and is accompanied by a low success rate. See text for details. MI, myocardial infarction; VT, ventricular tachycardia.

Primary VF in acute MI (not accompanied by low-output states) (**Chap. 41**) is generally very responsive to life support techniques and easily controlled after the initial event. In the in-hospital setting, respirator support is usually not necessary or is needed for only a short time, and hemodynamics stabilize promptly after defibrillation or cardioversion. In secondary VF in acute MI (those events in which hemodynamic abnormalities predispose to the potentially fatal arrhythmia), resuscitative efforts are less often successful, and in patients who are successfully resuscitated, the recurrence rate is high. The clinical picture and outcome are dominated by hemodynamic instability and the ability to control hemodynamic dysfunction. Bradyarrhythmias, asystole, and PEA are commonly secondary events in hemodynamically unstable patients.

The outcome after in-hospital cardiac arrest associated with noncardiac diseases is poor, and in the few successfully resuscitated patients, the postresuscitation course is dominated by the nature of the underlying disease. Patients with end-stage cancer, renal failure, acute central nervous system disease,

and uncontrolled infections, as a group, have a survival rate of <10% after in-hospital cardiac arrest. Some major exceptions are patients with transient airway obstruction, electrolyte disturbances, proarrhythmic effects of drugs, and severe metabolic abnormalities, most of whom may have a good chance of survival if they can be resuscitated promptly and stabilized while the transient abnormalities are being corrected.

LONG-TERM MANAGEMENT AFTER SURVIVAL OF OUT-OF-HOSPITAL CARDIAC ARREST Patients who survive cardiac arrest without irreversible damage to the central nervous system and who achieve hemodynamic stability should have diagnostic testing to define appropriate therapeutic interventions for their long-term management. This approach is driven by the fact that survival after out-of-hospital cardiac arrest is followed by a 10–25% mortality rate during the first 2 years after the event, and there are data suggesting that significant survival benefits can be achieved by prescription of an ICD.

Among patients in whom an acute ST elevation MI or transient and reversible myocardial ischemia is identified as the specific mechanism triggering an out-of-hospital cardiac arrest, the management is dictated in part by the transient nature of life-threatening arrhythmia risk during the acute coronary syndrome (ACS) and in part by the extent of permanent myocardial damage that results. Cardiac arrest during the acute ischemic phase is not an ICD indication, but survivors of cardiac arrest not associated with an ACS do benefit. In addition, patients who survive MI with an EF less than 30–35% appear to benefit from ICDs.

For patients with cardiac arrest determined to be due to a treatable transient ischemic mechanism, particularly with higher EFs, catheter interventional, surgical, and/or pharmacologic anti-ischemic therapy is generally accepted for long-term management.

Survivors of cardiac arrest due to other categories of disease, such as the hypertrophic or dilated cardiomyopathies and the various rare inherited disorders (e.g., right ventricular dysplasia, long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, and so-called idiopathic VF), are all considered ICD candidates.

PREVENTION OF SCD IN HIGH-RISK INDIVIDUALS WITHOUT PRIOR CARDIAC ARREST

Post-MI patients with EFs <35% and other markers of risk such as ambient ventricular arrhythmias, inducible ventricular tachyarrhythmias in the electrophysiology laboratory, and a history of heart failure are considered candidates for ICDs 40 days or more after the MI. Total mortality benefits in the range of a 20–35% reduction over 2–5 years have been observed in a series of clinical trials. One study suggested that an EF <30% was a sufficient marker of risk to indicate ICD benefit, and another demonstrated benefit for patients with Functional Class 2 or 3 heart failure and EFs ≤35%, regardless of etiology (ischemic or nonischemic) or the presence of ambient or induced arrhythmias (**Chaps. 18 and 19**). For patients with newly diagnosed heart failure and an EF <35%, the required delay between diagnosis and institution of medical therapy, and subsequent implantation of an ICD, is 90 days. In general, there appears to be a gradient of increasing ICD benefit with EFs ranging lower than the threshold indications. However, patients with very low EFs (e.g., <20%) may receive less benefit.

Decision making for primary prevention in disorders other than coronary artery disease and dilated cardiomyopathy is generally driven by observational data and judgment based on clinical observations. Controlled clinical trials providing evidence-based indicators for ICDs are lacking for these smaller population subgroups. In general, for the rare disorders listed above, indicators of arrhythmic risk such as syncope, documented ventricular tachyarrhythmias, aborted cardiac arrest, or a family history of premature SCD in some conditions, and a number of other clinical or ECG markers, may be used as indicators for ICDs.

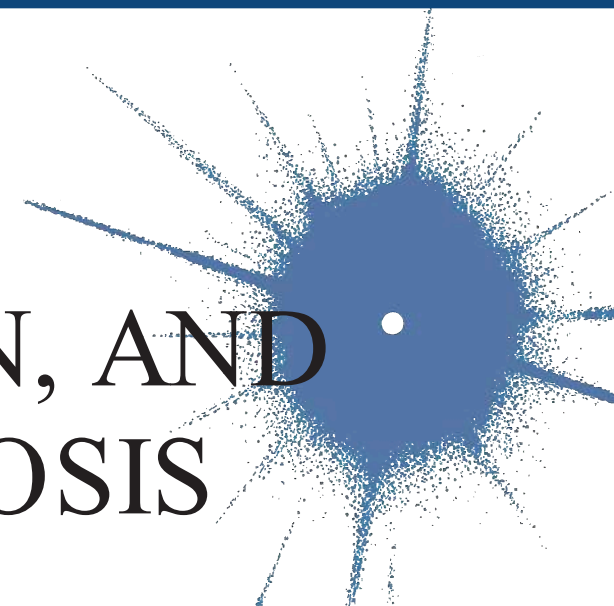
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SECTION V

DISORDERS OF THE
VASCULATURE

CHAPTER 36

THE PATHOGENESIS, PREVENTION, AND TREATMENT OF ATHEROSCLEROSIS



Peter Libby

PATHOGENESIS

Atherosclerosis remains the major cause of death and premature disability in developed societies. Moreover, current predictions estimate that by the year 2020 cardiovascular diseases, notably atherosclerosis, will become the leading global cause of total disease burden. Although many generalized or systemic risk factors predispose to its development, atherosclerosis affects various regions of the circulation preferentially and has distinct clinical manifestations that depend on the particular circulatory bed affected. Atherosclerosis of the coronary arteries commonly causes myocardial infarction (MI) (**Chap. 41**) and angina pectoris (**Chap. 39**). Atherosclerosis of the arteries supplying the central nervous system frequently provokes strokes and transient cerebral ischemia. In the peripheral circulation, atherosclerosis causes intermittent claudication and gangrene and can jeopardize limb viability. Involvement of the splanchnic circulation can cause mesenteric ischemia. Atherosclerosis can affect the kidneys either directly (e.g., renal artery stenosis) or as a common site of atheroembolic disease (**Chap. 46**).

Even within a particular arterial bed, stenoses due to atherosclerosis tend to occur focally, typically in certain predisposed regions. In the coronary circulation, for example, the proximal left anterior descending coronary artery exhibits a particular predilection for developing atherosclerotic disease. Similarly, atherosclerosis preferentially affects the proximal portions of the renal arteries and, in the extracranial circulation to the brain, the carotid bifurcation. Indeed, atherosclerotic lesions often form at branch points of arteries, regions characterized disturbed hydrodynamics. Not all manifestations of atherosclerosis result from stenotic, occlusive disease. Ectasia and the development of aneurysmal disease, for example, frequently occur in

the aorta (**Chap. 46**). In addition to focal, flow-limiting stenoses, nonocclusive intimal atherosclerosis also occurs diffusely in affected arteries, as shown by intravascular imaging and postmortem studies.

Atherogenesis in humans typically occurs over a period of many years, usually many decades. Growth of atherosclerotic plaques probably does not occur in a smooth, linear fashion but discontinuously, with periods of relative quiescence punctuated by periods of rapid evolution. After a generally prolonged “silent” period, atherosclerosis may become clinically manifest. The clinical expressions of atherosclerosis may be chronic, as in the development of stable, effort-induced angina pectoris or predictable and reproducible intermittent claudication. Alternatively, a dramatic acute clinical event such as MI, stroke, or sudden cardiac death may first herald the presence of atherosclerosis. Other individuals may never experience clinical manifestations of arterial disease despite the presence of widespread atherosclerosis demonstrated postmortem.

INITIATION OF ATHEROSCLEROSIS

An integrated view of experimental results in animals and studies of human atherosclerosis suggests that the “fatty streak” represents the initial lesion of atherosclerosis. These early lesions most often seem to arise from focal increases in the content of lipoproteins within regions of the intima. In particular, the fraction of lipoproteins related to low-density lipoprotein (LDL) that bear apolipoprotein B appear causally related to atherosclerosis. The accumulation of lipoprotein particles may not result simply from increased permeability, or “leakiness,” of the overlying endothelium (**Fig. 36-1**). Rather, the lipoproteins may collect in the intima of arteries because they bind to constituents of the extracellular matrix, increasing the residence time of the

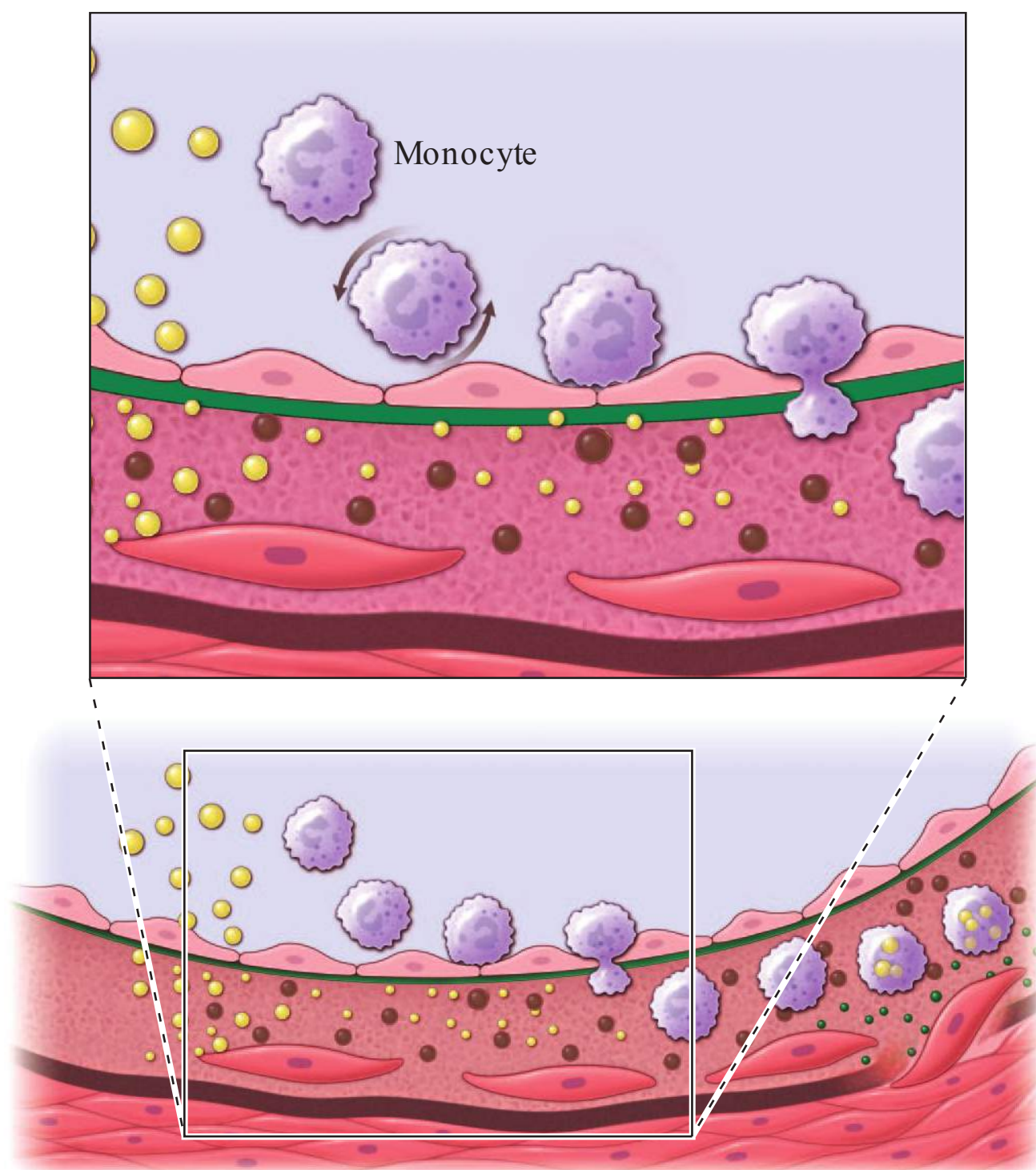


FIGURE 36-1

Cross-sectional view of an artery depicting steps in development of an atheroma, from left to right. The upper panel shows a detail of the boxed area below. The endothelial monolayer overlying the intima contacts blood. Hypercholesterolemia promotes accumulation of low-density lipoprotein (LDL) particles (yellow spheres) in the intima. The lipoprotein particles often associate with constituents of the extracellular matrix, notably proteoglycans. Sequestration within the intima separates lipoproteins from some plasma antioxidants and favors oxidative modification. Such modified lipoprotein particles (darker spheres) may trigger a local inflammatory response that signals subsequent steps in lesion formation. The augmented expression of various adhesion molecules for leukocytes recruits monocytes to the site of a nascent arterial lesion.

Once adherent, some white blood cells migrate into the intima. The directed migration of leukocytes probably depends on chemoattractant factors, including modified lipoprotein particles themselves and chemoattractant cytokines (depicted by the smaller green spheres), such as the chemokine macrophage chemoattractant protein-1 produced by vascular wall cells in response to modified lipoproteins. Leukocytes in the evolving fatty streak can divide and exhibit augmented expression of receptors for modified lipoproteins (scavenger receptors). These mononuclear phagocytes ingest lipids and become foam cells, represented by a cytoplasm filled with lipid droplets. As the fatty streak evolves into a more complicated atherosclerotic lesion, smooth-muscle cells migrate from the media (bottom of lower panel hairline) through the internal elastic membrane (solid wavy line) and accumulate within the expanding intima, where they lay down extracellular matrix that forms the bulk of the advanced lesion (bottom panel, right side).

lipid-rich particles within the arterial wall. Lipoproteins that accumulate in the extracellular space of the intima of arteries often associate with proteoglycans of the arterial extracellular matrix, an interaction that may slow the egress of these lipid-rich particles from the intima. Lipoprotein particles in the extracellular space of the intima, particularly those retained by binding to matrix macromolecules, may undergo oxidative modifications. Considerable evidence supports a pathogenic role for products of oxidized lipoproteins in atherogenesis. Lipoproteins sequestered from (plasma) antioxidants in the extracellular space of the intima become particularly susceptible to oxidative modification, giving rise to hydroperoxides, lysophospholipids, oxysterols, and aldehydic breakdown products of fatty acids and phospholipids. Modifications of the apoprotein moieties may include breaks in the peptide backbone as well as derivatization of certain amino acid residues. Local production of hypochlorous acid by myeloperoxidase associated with inflammatory cells within the plaque yields chlorinated species such as chlorotyrosyl moieties. Considerable evidence supports the presence of such oxidation products in atherosclerotic lesions.

Leukocyte recruitment

Accumulation of leukocytes characterizes the formation of early atherosclerotic lesions (Fig. 36-1). Thus, from its very inception, atherogenesis involves elements of inflammation, a process that now provides a unifying theme in the pathogenesis of this disease. The inflammatory cell types typically found in the evolving atheroma include monocyte-derived macrophages and dendritic cells, T and B lymphocytes, and mast cells. Hypercholesterolemia augments the portion of particularly proinflammatory monocytes in blood that preferentially enter the nascent atheroma in mice. A number of adhesion molecules or receptors for leukocytes expressed on the surface of the arterial endothelial cell probably participate in the recruitment of leukocytes to the nascent atheroma. Proinflammatory cytokines can augment the expression of leukocyte adhesion molecules.

Laminar shear forces such as those encountered in most regions of normal arteries also can suppress the expression of leukocyte adhesion molecules. Sites of predilection for atherosclerotic lesions (e.g., distal to flow dividers) often have low shear stress and/or disturbed flow. Ordered, pulsatile laminar shear of normal blood flow augments the production of nitric oxide by endothelial cells. This molecule, in addition to its vasodilator properties, can act at the low levels constitutively produced by arterial endothelium as a local anti-inflammatory autacoid, e.g., limiting local adhesion molecule expression. Exposure of endothelial cells to laminar shear stress increases the transcription of Krüppel-like

factor 2 (KLF2), which augments the activity of numerous salutary endothelial functions including nitric oxide synthase. Laminar shear stress also stimulates endothelial cells to produce superoxide dismutase, an antioxidant enzyme. These examples indicate how hemodynamic forces may influence the cellular events that underlie atherosclerotic lesion initiation and potentially explain the favored localization of atherosclerotic lesions at sites that experience disturbed flow or low shear stress.

Once captured on the surface of the arterial endothelial cell by adhesion receptors, the leukocytes penetrate the endothelial layer and take up residence in the intima. In addition to products of modified lipoproteins, cytokines (protein mediators of inflammation) can regulate the expression of adhesion molecules involved in leukocyte recruitment. For example, interleukin 1 (IL-1) and tumor necrosis factor (TNF) induce or augment the expression of leukocyte adhesion molecules on endothelial cells. Because products of lipoprotein oxidation can induce cytokine release from vascular wall cells, this pathway may provide an additional link between arterial accumulation of lipoproteins and leukocyte recruitment. Chemoattractant cytokines appear to direct the migration of leukocytes into the arterial wall.

Foam-cell formation

Once resident within the intima, the mononuclear phagocytes mature into macrophages and become lipid-laden foam cells, a conversion that requires the uptake of lipoprotein particles by receptor-mediated endocytosis. One might suppose that the “classic” LDL receptor mediates this lipid uptake; however, humans or animals lacking effective LDL receptors due to genetic alterations (e.g., familial hypercholesterolemia) have abundant arterial lesions and extraarterial xanthomata rich in macrophage-derived foam cells. In addition, the exogenous cholesterol suppresses expression of the LDL receptor; thus, the level of this cell-surface receptor for LDL decreases under conditions of cholesterol excess. Candidates for alternative receptors that can mediate lipid loading of foam cells include a number of macrophage “scavenger” receptors, which preferentially endocytose modified lipoproteins, and other receptors for oxidized LDL or very low-density lipoprotein (VLDL). Monocyte attachment to the endothelium, migration into the intima, and maturation to form lipid-laden macrophages thus represent key steps in the formation of the fatty streak, the precursor of fully formed atherosclerotic plaques.

ATHEROMA EVOLUTION AND COMPLICATIONS

Although the fatty streak commonly precedes the development of a more advanced atherosclerotic plaque, not all fatty streaks progress to form complex atheromata.

By ingesting lipids from the extracellular space, the mononuclear phagocytes bearing such scavenger receptors may remove lipoproteins from the developing lesion. Some lipid-laden macrophages may leave the artery wall, exporting lipid in the process. Lipid accumulation, and hence the propensity to form an atheroma, ensues if the amount of lipid entering the artery wall exceeds that removed by mononuclear phagocytes or other pathways. Macrophages also proliferate in plaques in response to hematopoietic growth factors overexpressed in lesions, another aspect of the dynamic regulation and flux of cells during atherogenesis.

Export by phagocytes may constitute one response to local lipid overload in the evolving lesion. Another mechanism, reverse cholesterol transport mediated by high-density lipoproteins (HDLs), probably provides an independent pathway for lipid removal from atheroma. This transfer of cholesterol from the cell to the HDL particle involves specialized cell-surface molecules such as the ATP binding cassette (ABC) transporters. ABCA1, the gene mutated in Tangier disease, a condition characterized by very low HDL levels, transfers cholesterol from cells to nascent HDL particles and ABCG1 to mature HDL particles. “Reverse cholesterol transport” mediated by these ABC transporters allows HDL loaded with cholesterol to deliver it to hepatocytes by binding to scavenger receptor B1 or other receptors. The liver cell can metabolize the sterol to bile acids that can be excreted. Thus, macrophages may play a vital role in the dynamic economy of lipid accumulation in the arterial wall during atherogenesis.

Some lipid-laden foam cells within the expanding intimal lesion perish. Some foam cells may die as a result of programmed cell death, or apoptosis. This death of mononuclear phagocytes results in the formation of the lipid-rich center, often called the necrotic core, in established atherosclerotic plaques. Impaired clearance of dead foam cells (efferocytosis) in plaques may hasten lipid core formation. Macrophages loaded with modified lipoproteins may elaborate microparticles or exosomes (which may contain regulatory microRNAs), cytokines, and growth factors that can further signal some of the cellular events in lesion complication. Whereas accumulation of lipid-laden macrophages characterizes the fatty streak, buildup of fibrous tissue formed by extracellular matrix typifies the more advanced atherosclerotic lesion. The smooth-muscle cell synthesizes the bulk of the extracellular matrix of the complex atherosclerotic lesion. A number of growth factors or cytokines elaborated by mononuclear phagocytes can stimulate smooth-muscle cell proliferation and production of extracellular matrix. Cytokines found in the plaque, including IL-1 and TNF, can induce local production of growth factors, including forms of platelet-derived growth factor (PDGF), fibroblast growth factors, and others, which may contribute to plaque evolution and complication. Other cytokines, notably interferon γ (IFN- γ) derived

from activated T cells within lesions, can limit the synthesis of interstitial forms of collagen by smooth-muscle cells. These examples illustrate how atherogenesis involves a complex mix of mediators that in the balance determines the characteristics of particular lesions.

The accumulation of smooth-muscle cells and their elaboration of extracellular matrix probably provide a critical transition, yielding a fibrofatty lesion in place of a simple accumulation of macrophage-derived foam cells. For example, PDGF elaborated by activated platelets, macrophages, and endothelial cells can stimulate the migration of smooth-muscle cells normally resident in the tunica media into the intima. Such growth factors and cytokines produced locally can stimulate the proliferation of resident smooth-muscle cells or resident stem cells in the intima as well as those that may migrate in from the media. Transforming growth factor β (TGF- β), among other mediators, potently stimulates interstitial collagen production by smooth-muscle cells. These mediators may arise not only from neighboring vascular cells or leukocytes (a “paracrine” pathway), but also, in some instances, from the same cell that responds to the factor (an “autocrine” pathway). Together, these alterations in smooth-muscle cells, signaled by these mediators acting at short distances, can hasten transformation of the fatty streak into a more fibrous smooth-muscle cell and extracellular matrix—rich lesion.

In addition to locally produced mediators, products of blood coagulation and thrombosis likely contribute to atheroma evolution and complication. This involvement justifies the use of the term atherothrombosis to convey the inextricable links between atherosclerosis and thrombosis. Fatty streak formation begins beneath a morphologically intact endothelium. In advanced fatty streaks, however, microscopic breaches in endothelial integrity may occur. Microthrombi rich in platelets can form at such sites of limited endothelial denudation, owing to exposure of the thrombogenic extracellular matrix of the underlying basement membrane. Activated platelets release numerous factors that can promote the fibrotic response, including PDGF and TGF- β . Thrombin not only generates fibrin during coagulation, but also stimulates protease-activated receptors that can signal smooth-muscle migration, proliferation, and extracellular matrix production. Many arterial mural microthrombi resolve without clinical manifestation by a process of local fibrinolysis, resorption, and endothelial repair, yet can lead to lesion progression by stimulating these profibrotic functions of smooth-muscle cells (Fig. 36-2D).

Microvessels

As atherosclerotic lesions advance, abundant plexi of microvessels develop in connection with the artery's vasa vasorum. Newly developing microvascular networks may

contribute to lesion complications in several ways. These blood vessels provide an abundant surface area for leukocyte trafficking and may serve as the portal for entry and exit of white blood cells from the established atheroma. Microvessels in the plaques may also furnish foci for intraplaque hemorrhage. Like the neovessels in the diabetic retina, microvessels in the atheroma may be friable and prone to rupture and can produce focal hemorrhage. Such a vascular leak can provoke thrombosis in situ, yielding local thrombin generation, which in turn can activate smooth-muscle and endothelial cells through ligation of protease-activated receptors. Atherosclerotic plaques often contain fibrin and hemosiderin, an indication that episodes of intraplaque hemorrhage contribute to plaque complications.

Calcification

As they advance, atherosclerotic plaques also accumulate calcium. Microvesicles derived from lesional cells can stimulate calcification, and this process co-localizes with regions of heightened inflammation. Mineralization of the atherosclerotic plaque recapitulates many aspects of bone formation, including the regulatory participation of transcription factors such as Runx2.

Plaque evolution

Smooth-muscle cells and macrophages die in the atherosclerotic plaque. Indeed, complex atheromata often have a mostly fibrous character and lack the cellularity of less advanced lesions. This relative paucity of smooth-muscle cells in advanced atheromata may result from the predominance of cytostatic mediators such as TGF- β and IFN- γ (which can inhibit smooth-muscle cell proliferation) and also from smooth-muscle cell apoptosis. Thus, during the evolution of the atherosclerotic plaque, a complex and highly regulated balance between entry and egress of lipoproteins and leukocytes, cell proliferation and cell death, extracellular matrix production, and remodeling, as well as calcification and neovascularization, contribute to lesion formation. Many mediators related to atherogenic risk factors, including those derived from lipoproteins, cigarette smoking, and angiotensin II, provoke the production of proinflammatory cytokines and alter the behavior of the intrinsic vascular wall cells and infiltrating leukocytes that underlie the complex pathogenesis of these lesions. Thus, advances in vascular biology have led to increased understanding of the mechanisms that link risk factors to the pathogenesis of atherosclerosis and its complications.

PATHOPHYSIOLOGIC CONSEQUENCES OF ATHEROSCLEROSIS

Atherosclerotic lesions occur ubiquitously in Western societies, and the prevalence of this disease is on

the rise globally. Most atheromata produce no symptoms, and many never cause clinical manifestations. Numerous patients with diffuse atherosclerosis may succumb to unrelated illnesses without ever having

experienced a clinically significant manifestation of atherosclerosis. Arterial remodeling during atheroma formation accounts for some of this variability in the clinical expression of atherosclerotic disease (**Fig. 36-2A**).

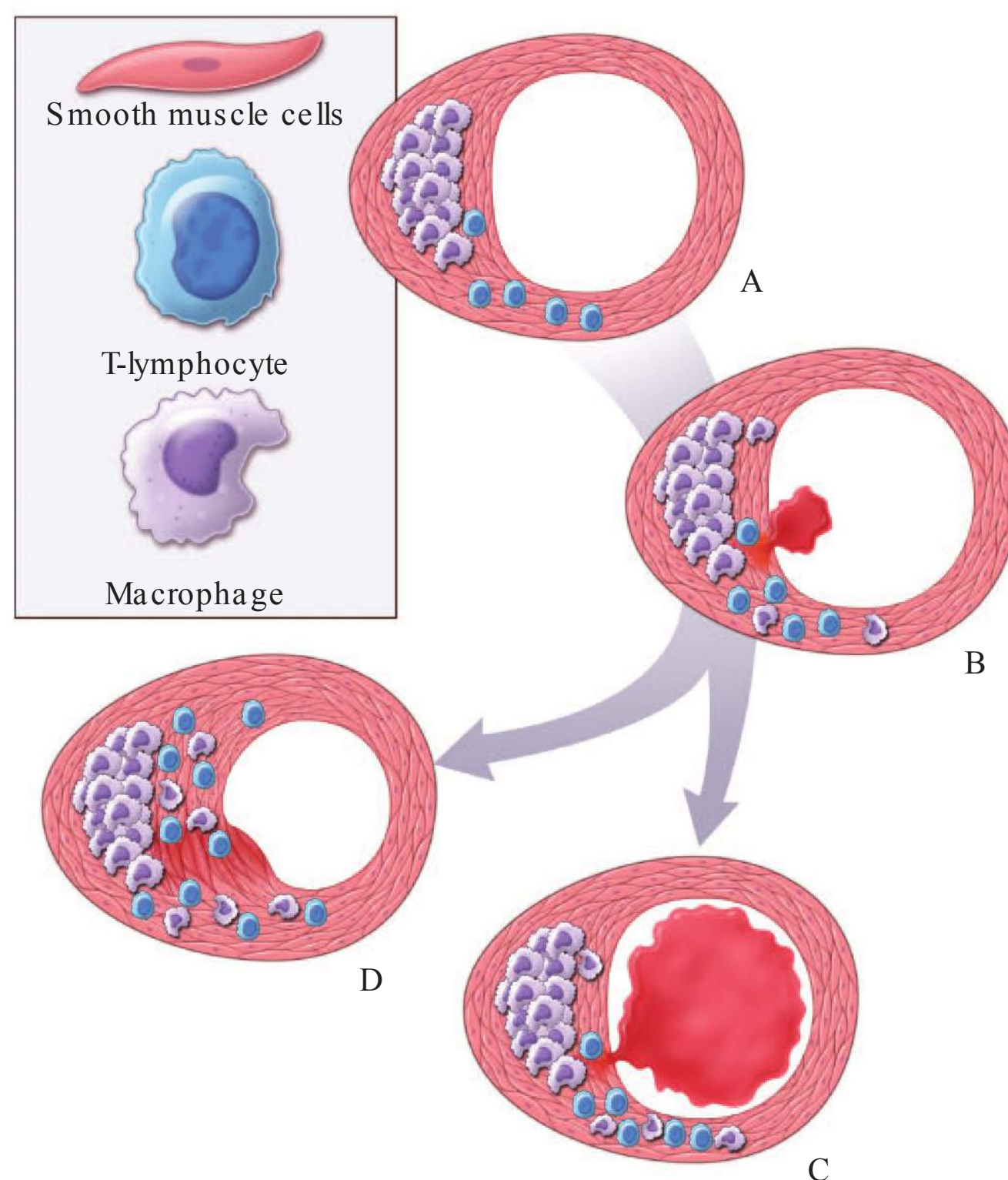


FIGURE 36-2

Plaque rupture, thrombosis, and healing. A. Arterial remodeling during atherogenesis. During the initial part of the life history of an atheroma, growth is often outward, preserving the caliber of the lumen. This phenomenon of “compensatory enlargement” accounts in part for the tendency of coronary arteriography to underestimate the degree of atherosclerosis. B. Rupture of the plaque’s fibrous cap causes thrombosis. Physical disruption of the atherosclerotic plaque commonly causes arterial thrombosis by allowing blood coagulant factors to contact thrombogenic collagen found in the arterial extracellular matrix and tissue factor produced by macrophage-derived foam cells in the lipid core of lesions. In this manner, sites of plaque rupture form the nidus for thrombi. The normal artery wall has several fibrinolytic or anti-thrombotic mechanisms that tend to resist thrombosis and lyse clots that begin to form in situ. Such antithrombotic or thrombolytic molecules include thrombomodulin, tissue- and urokinase-type plasminogen activators, heparan sulfate proteoglycans, prostacyclin, and nitric oxide. C. When the clot overwhelms the endogenous fibrinolytic mechanisms, it may propagate and lead to arterial occlusion. The consequences of this occlusion depend on the degree of existing collateral vessels. In a patient with chronic multivessel occlusive coronary artery disease (CAD), collateral channels have often formed. In such circumstances, even a

total arterial occlusion may not lead to myocardial infarction (MI), or it may produce an unexpectedly modest or a non-ST-segment elevation infarct because of collateral flow. In a patient with less advanced disease and without substantial stenotic lesions to provide a stimulus for collateral vessel formation, sudden plaque rupture and arterial occlusion commonly produces an ST-segment elevation infarction. These are the types of patients who may present with MI or sudden death as a first manifestation of coronary atherosclerosis. In some cases, the thrombus may lyse or organize into a mural thrombus without occluding the vessel. Such instances may be clinically silent. D. The subsequent thrombin-induced fibrosis and healing causes a fibroproliferative response that can lead to a more fibrous lesion that can produce an eccentric plaque that causes a hemodynamically significant stenosis. In this way, a nonocclusive mural thrombus, even if clinically silent or causing unstable angina rather than infarction, can provoke a healing response that can promote lesion fibrosis and luminal encroachment. Such a sequence of events may convert a “vulnerable” atheroma with a thin fibrous cap that is prone to rupture into a more “stable” fibrous plaque with a reinforced cap. Angioplasty of unstable coronary lesions may “stabilize” the lesions by a similar mechanism, producing a wound followed by healing.

During the initial phases of atheroma development, the plaque usually grows outward, in an abluminal direction. Vessels affected by atherogenesis tend to increase in diameter, a phenomenon known as compensatory enlargement, a type of vascular remodeling. The growing atheroma does not encroach on the arterial lumen until the burden of atherosclerotic plaque exceeds ~40% of the area encompassed by the internal elastic lamina. Thus, during much of its life history, an atheroma will not cause stenosis that can limit tissue perfusion.

Flow-limiting stenoses commonly form later in the history of the plaque. Many such plaques cause stable syndromes such as demand-induced angina pectoris or intermittent claudication in the extremities. In the coronary circulation and other circulations, even total vascular occlusion by an atheroma does not invariably lead to infarction. The hypoxic stimulus of repeated bouts of ischemia characteristically induces formation of collateral vessels in the myocardium, mitigating the consequences of an acute occlusion of an epicardial coronary artery. By contrast, many lesions that cause acute or unstable atherosclerotic syndromes, particularly in the coronary circulation, may arise from atherosclerotic plaques that do not produce a flow-limiting stenosis. Such lesions may produce only minimal luminal irregularities on traditional angiograms and often do not meet the traditional criteria for “significance” by arteriography. Thrombi arising from such nonocclusive stenoses may explain the frequency of MI as an initial manifestation of coronary artery disease (CAD) (in at least one-third of cases) in patients who report no prior history of angina pectoris, a syndrome usually caused by flow-limiting stenoses.

Plaque instability and rupture

Postmortem studies afford considerable insight into the microanatomic substrate underlying the “instability” of plaques that do not cause critical stenoses. A superficial erosion of the endothelium or a frank plaque rupture or fissure usually produces the thrombus that causes episodes of unstable angina pectoris or the occlusive and relatively persistent thrombus that causes acute MI (Fig. 36-2B). Rupture of the plaque’s fibrous cap (Fig. 36-2C) permits contact between coagulation factors in the blood and highly thrombogenic tissue factor expressed by macrophage foam cells in the plaque’s lipid-rich core. If the ensuing thrombus is nonocclusive or transient, the episode of plaque disruption may not cause symptoms or may result in episodic ischemic symptoms such as rest angina. Occlusive thrombi that endure often cause acute MI, particularly in the absence of a well-developed collateral circulation that supplies

the affected territory. Repetitive episodes of plaque disruption and healing provide one likely mechanism of transition of the fatty streak to a more complex fibrous lesion (Fig. 36-2D). The healing process in arteries, as in skin wounds, involves the laying down of new extracellular matrix and fibrosis.

Not all atheromata exhibit the same propensity to rupture. Pathologic studies of culprit lesions that have caused acute MI reveal several characteristic features. Plaques that have caused thromboses tend to have thin fibrous caps, relatively large lipid cores, a high content of macrophages, outward remodeling, and spotty (rather than dense) calcification. Morphometric studies of such culprit lesions show that at sites of plaque rupture, macrophages and T lymphocytes predominate and contain relatively few smooth-muscle cells. The cells that concentrate at sites of plaque rupture bear markers of inflammatory activation. In addition, patients with active atherosclerosis and acute coronary syndromes display signs of disseminated inflammation. Inflammatory mediators regulate processes that govern the integrity of the plaque’s fibrous cap and, hence, its propensity to rupture. For example, the T cell–derived cytokine IFN- γ , which is found in atherosclerotic plaques, can inhibit growth and collagen synthesis of smooth-muscle cells, as noted above. Cytokines derived from activated macrophages and lesional T cells can boost production of proteolytic enzymes that can degrade the extracellular matrix of the plaque’s fibrous cap. Thus, inflammatory mediators can impair the collagen synthesis required for maintenance and repair of the fibrous cap and trigger degradation of extracellular matrix macromolecules, processes that weaken the plaque’s fibrous cap and enhance its susceptibility to rupture (so-called vulnerable plaques, Fig. 36-3). In contrast to plaques with these features of vulnerability, those with a dense extracellular matrix and relatively thick fibrous cap without substantial tissue factor–rich lipid cores seem generally resistant to rupture and unlikely to provoke thrombosis.

Functional features of the atheromatous plaque, in addition to its degree of luminal encroachment, influence the clinical manifestations of this disease. This enhanced understanding of plaque biology provides insight into the diverse ways in which atherosclerosis can present clinically and the reasons why the disease may remain silent or stable for prolonged periods, punctuated by acute complications at certain times. Increased understanding of atherogenesis provides new insight into the mechanisms linking it to the risk factors discussed below, indicates the ways in which current therapies may improve outcomes, and suggests new targets for future intervention.

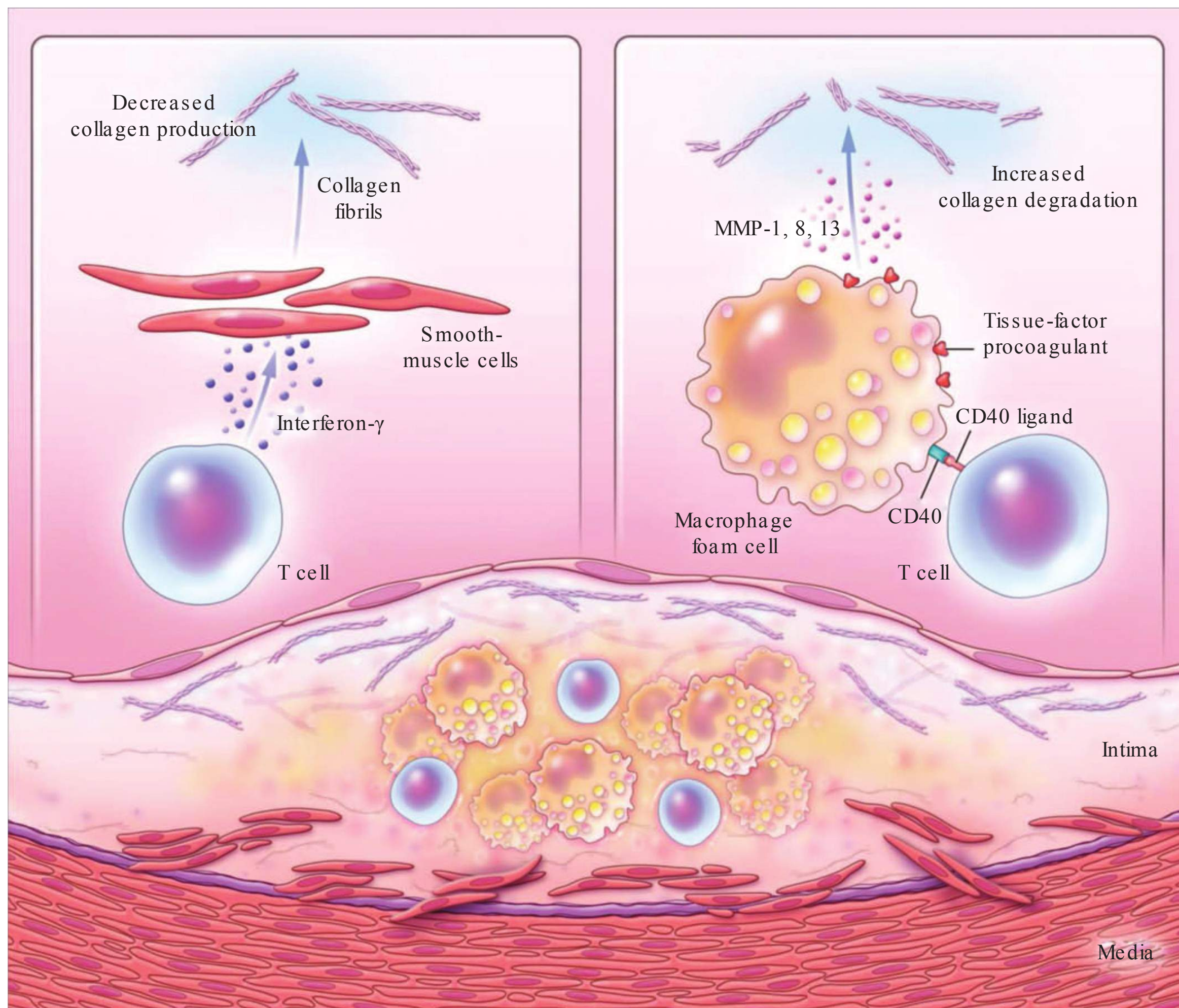


FIGURE 36-3

Inflammatory pathways that predispose atherosclerotic plaques to rupture and provoke thrombosis. A cross-section of an atheromatous plaque at the bottom of the figure shows the central lipid core that contains macrophage foam cells (yellow) and T cells (blue). The intima and media also contain arterial smooth-muscle cells (red), which are the source of arterial collagen (depicted as triple helical coiled structures). Activated T cells (of the type 1 helper T cell subtype) secrete cytokine interferon γ , which inhibits the production of the new, interstitial collagen that is required to repair and maintain the plaque's protective fibrous cap (upper left). The T cells can also activate the macrophages in the intimal lesion by expressing the inflammatory mediator CD40 ligand (CD154), which engages its cognate receptor (CD40) on

the phagocyte. This inflammatory signalling causes overproduction of interstitial collagenases (matrix metalloproteinases [MMPs] 1, 8, and 13) that catalyze the initial rate-limiting step in collagen breakdown (top right). CD40 ligation also causes macrophages to overproduce tissue-factor procoagulant. Thus, inflammatory signalling puts the collagen in the plaque's fibrous cap in double jeopardy—decreasing synthesis and increasing breakdown—rendering the cap susceptible to rupture. Inflammatory activation also boosts tissue-factor production, which triggers thrombus formation in the disrupted plaque. These mechanisms link inflammation in the plaque to the thrombotic complications of atherosclerosis, including the acute coronary syndromes. (Adapted from P Libby: *N Engl J Med* 368:2004, 2013.)

PREVENTION AND TREATMENT

THE CONCEPT OF ATHEROSCLEROTIC RISK FACTORS

The systematic study of risk factors for atherosclerosis emerged from a coalescence of experimental results, as well as from cross-sectional and ultimately longitudinal studies in humans. The prospective, community-based Framingham Heart Study provided rigorous support for the concept that hypercholesterolemia, hypertension,

and other factors correlate with cardiovascular risk. Similar observational studies performed worldwide bolstered the concept of “risk factors” for cardiovascular disease.

From a practical viewpoint, the cardiovascular risk factors that have emerged from such studies fall into two categories: those modifiable by lifestyle and/or pharmacotherapy, and those that are immutable, such as age and sex. The weight of evidence supporting various risk factors differs. For example, hypercholesterolemia and hypertension certainly

predict coronary risk, but the magnitude of the contributions of other so-called nontraditional risk factors, such as levels of homocysteine, levels of lipoprotein (a) [Lp(a)], and infection, remains controversial. Moreover, some biomarkers that predict cardiovascular risk may not participate in the causal pathway for the disease or its complications. Genetic studies using genome-wide association (GWAS) approaches and Mendelian randomization approaches have helped to distinguish between risk markers and factors that contribute causally to the disease. For example, recent genetic studies suggest that C-reactive protein (CRP) does not itself mediate atherogenesis, despite its ability to predict risk, whereas Lp(a) and apolipoprotein C3 have emerged as a causal risk factor. **Table 36-1** lists a number of risk factors implicated in atherosclerosis. The sections below will consider some of these factors and approaches to their modification.

Lipid disorders

Abnormalities in plasma lipoproteins and derangements in lipid metabolism rank among the most firmly established and best understood risk factors for atherosclerosis. **Chapter 37 describes the lipoprotein classes and provides a detailed discussion of lipoprotein metabolism.**

TABLE 36-1

MAJOR RISK FACTORS FOR ATHEROSCLEROSIS	
High LDL cholesterol	
Cigarette smoking	
Hypertension (BP $\geq 140/90$ mmHg or on antihypertensive medication)	
Low HDL cholesterol ^a (<1.0 mmol/L [<40 mg/dL])	
Diabetes mellitus	
Family history of premature CHD	
Age (men ≥ 45 years; women ≥ 55 years)	
Lifestyle risk factors	
Obesity (BMI ≥ 30 kg/m ²)	
Physical inactivity	
Atherogenic diet	
Emerging risk factors	
Lipoprotein (a)	
Prothrombotic factors	
Proinflammatory factors	
Impaired fasting glucose	
Subclinical atherosclerosis	

^aHDL cholesterol ≥ 1.6 mmol/L (≥ 60 mg/dL) has been viewed as a “negative” risk factor.

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

The American College of Cardiology and American Heart Association (ACC/AHA) promulgated new guidelines on risk assessment, lifestyle measures, and cholesterol management in 2013. The panels that produced these guidelines followed an evidence-based approach. The 2013 cholesterol guideline focused on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) rather than other classes of lipid-modulating drugs, including fibric acid derivatives, cholesterol absorption inhibitors such as ezetimibe, and niacin products. The guideline cites the lack of contemporary randomized clinical trial evidence that supports the efficacy of these nonstatin lipid-modifying agents in cardiovascular event reduction. The cholesterol guideline defined four statin benefit groups (**Table 36-2**): (1) all individuals who have clinical atherosclerotic cardiovascular disease (ASCVD), therefore considered “secondary prevention”; (2) those with LDL cholesterol ≥ 190 mg/dL without a secondary cause such as a high intake of saturated or trans fats, various drugs, or certain diseases; (3) individuals with diabetes without established cardiovascular disease who are 40–75 years old and have LDL cholesterol of 70–189 mg/dL; and (4) those without established ASCVD without diabetes who are 40–75 years old and who have LDL cholesterol of 70–189 mg/dL and a calculated ASCVD risk $\geq 7.5\%$. An online risk calculator based on pooled cohorts was provided to aid clinicians and patients in calculating their risk (http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp). Other validated risk calculators that incorporate family history of CAD and a marker of inflammation (high-sensitivity CRP [hsCRP]) that apply to U.S. women and men exist (<http://www.reynoldsriskscore.org>). Downloadable applications for risk calculation on handheld devices are readily available.

TABLE 36-2

SUMMARY OF THE FOUR STATIN BENEFIT GROUPS DESCRIBED IN THE 2013 ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK IN ADULTS

- Clinical ASCVD “secondary prevention”
- LDL-C ≥ 190 mg/dL without secondary cause (e.g., saturated/trans fats, drugs, certain diseases)
- Primary prevention with diabetes mellitus: age 40–75 years, LDL-C 70–189 mg/dL
- Primary prevention without diabetes mellitus: age 40–75 years, LDL-C 70–189 mg/dL, estimated ASCVD risk $\geq 7.5\%$

Abbreviations: ACC/AHA, American College of Cardiology and American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Source: Adapted from NJ Stone et al: 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. J Am Coll Cardiol 2013, doi: 10.1016/j.jacc.2013.11.002.

The 2013 guideline emphasized a patient-centered approach and recommended that clinicians and patients engage in a risk-benefit conversation before starting statin therapy and not rely solely on calculated risks or arbitrary category assignment. It further emphasizes that medications do not supplant a healthy lifestyle. The guideline also provides some practical suggestions regarding management of muscle symptoms attributed to statins, an issue of considerable concern to many patients and practitioners alike.

In a major departure from prior guidelines, the 2013 guideline eliminates LDL targets as goals of therapy. The panel did so because major clinical trials did not titrate therapy to a goal, but rather used fixed doses of statins. Instead, the new guideline suggests different intensities of statin therapy based on risk category (Fig. 36-4). The 2013 guideline focus on statins reflects an extensive body of rigorous evidence that supports the effectiveness of this class of drugs in cardiovascular event

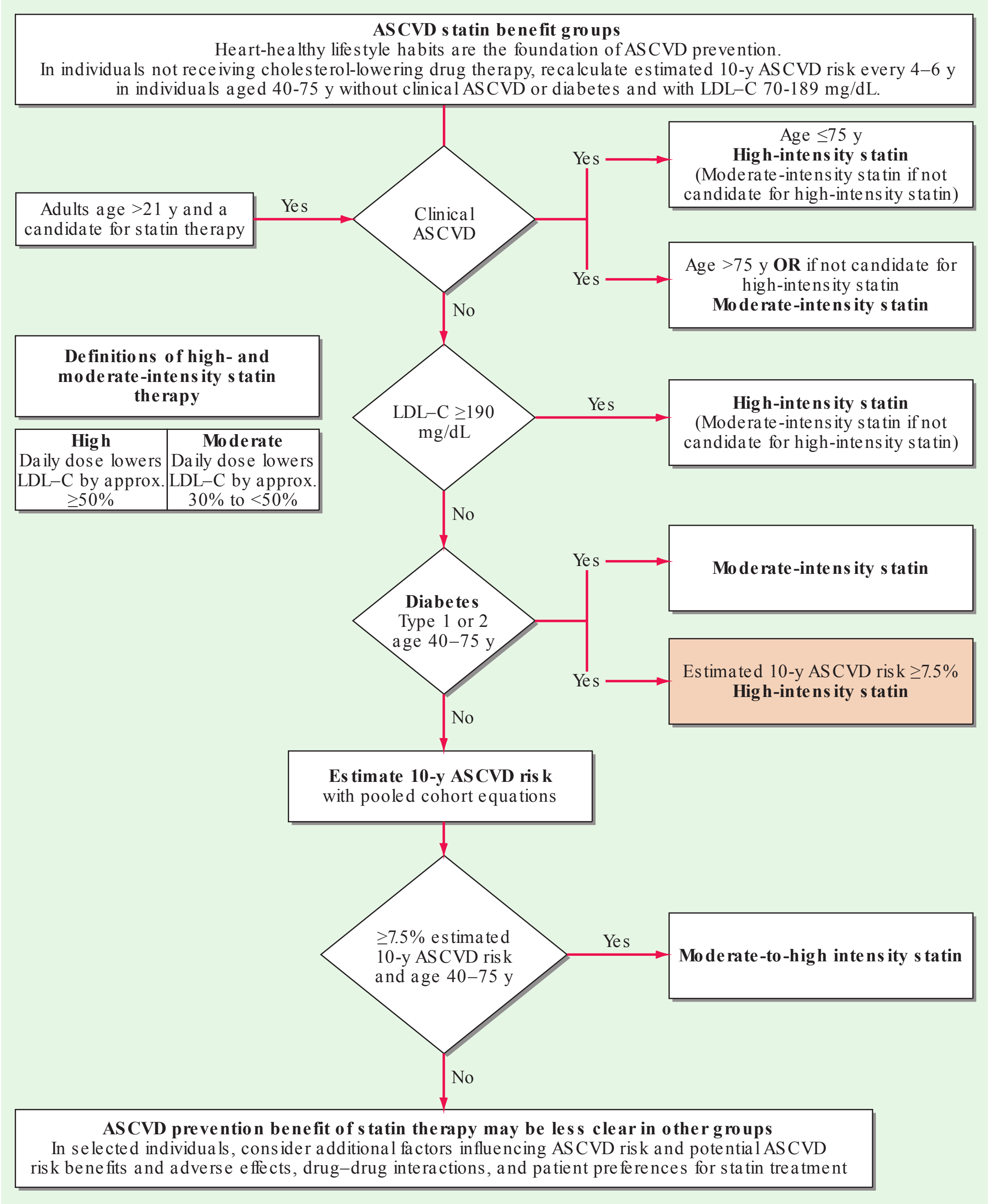


FIGURE 36-4
Major recommendations for statin therapy for atherosclerotic cardiovascular disease (ASCVD) prevention. LDL-C, low-density

lipoprotein cholesterol. (From NJ Stone et al: J Am Coll Cardiol, 2013, doi: 10.1016/j.jacc.2013.11.002.)

reduction and an acceptable risk-benefit relationship (Fig. 36-5). Moreover, because almost all statins are now available as generic statins medications, cost has become much less of an impediment to their use.

The clinical use of effective pharmacologic strategies for lowering LDL has reduced cardiovascular events markedly, but a considerable burden of residual risk remains even in patients treated with high-intensity statins. Hence, current studies are evaluating other avenues to address the residual burden of cardiovascular disease that persists despite statin treatment. Inhibitors of genetic studies identified proprotein convertase subtilisin kexin-like 9 (PCSK9) as a regulator of LDL levels associated with cardiovascular outcomes. Interaction of the LDL receptor with PCSK9 hastens the receptor's degradation, and hence yields higher circulating LDL concentrations. Genetic variants that lower PCSK9 activity appear to protect against cardiovascular events. Monoclonal antibodies that neutralize PCSK9 lower LDL levels even in statin-treated patients and are currently under investigation as novel therapeutics to lower cardiovascular risk.

LDL-lowering therapies do not appear to exert their beneficial effect on cardiovascular events by causing a marked "regression" of stenoses. Studies of lipid lowering monitored by angiography or by intravascular imaging modalities have shown at best a modest reduction in coronary artery stenoses over the duration of study, despite abundant evidence of event reduction. These results suggest that the beneficial mechanism of lipid lowering by statins does not require a substantial reduction in the fixed stenoses. Rather, the benefit may derive from "stabilization" of atherosclerotic lesions without substantially decreased stenosis. Such stabilization of atherosclerotic lesions and the attendant decrease in coronary events may result from the egress of lipids or from favorably influencing aspects of the biology of atherogenesis discussed above. In addition, as sizable lesions may protrude abuminally rather than into the lumen due to complementary enlargement, shrinkage of such plaques may not be apparent on angiograms. The consistent benefit of statins may depend not only on their salutary effects on the lipid profile, but also on direct modulation of plaque biology independent of lipid lowering.

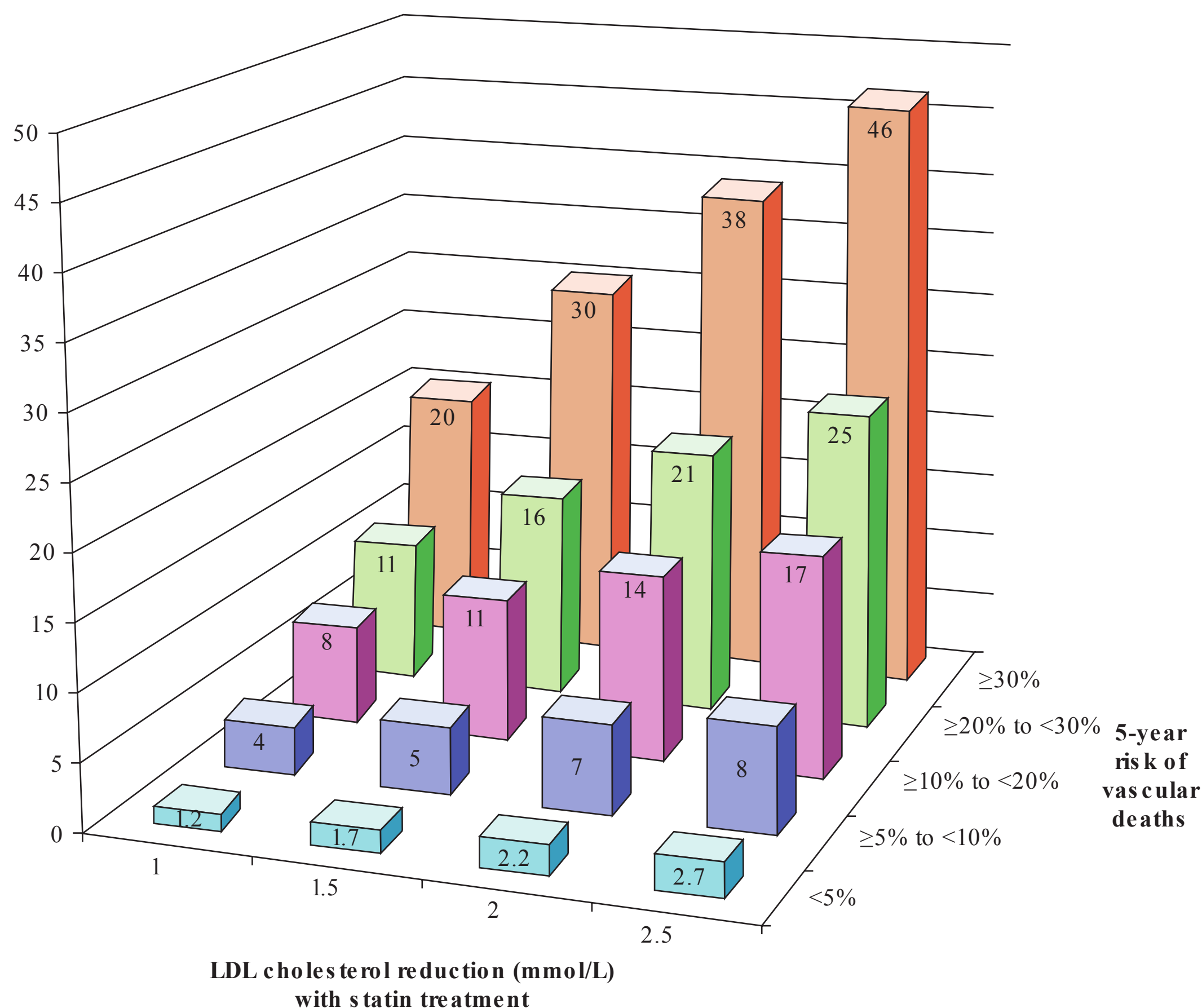


FIGURE 36-5

The Cholesterol Treatment Trialists Collaboration meta-analyzed 27 randomized clinical trials evaluating statin therapy. They found profound decreases in both major vascular events and vascular death (not shown) proportional to the magnitude of

low-density lipoprotein (LDL) cholesterol reduction achieved with statin treatment. This diagram shows the results of this meta-analysis for vascular death. (From Lancet 380:581, 2012.)

TABLE 36-3

HEART HEALTHY NUTRITION AND PHYSICAL ACTIVITY BEHAVIORS RECOMMENDED IN THE 2013 ACC/AHA GUIDELINE ON LIFESTYLE MANAGEMENT TO REDUCE CARDIOVASCULAR RISK
The adult population should be encouraged to practice heart healthy lifestyle behaviors, including: • Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; include low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limit intake of sodium, sweets, sugar-sweetened beverages, and red meats. • Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus). • Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet. • Engage in 2 h and 30 min a week of moderate-intensity or 1 h and 15 min (75 min) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 min, preferably spread throughout the week. • Achieve and maintain a healthy weight. Refer to the 2013 Obesity Expert Panel Report for recommendations on weight loss and maintenance.

Abbreviations: ACC/AHA, American College of Cardiology and American Heart Association; DASH, Dietary Approaches to Stop Hypertension; USDA, U.S. Department of Agriculture.
Source: Adapted from RH Eckel et al: 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk. J Am Coll Cardiol 2013, doi: 10.1016/j.jacc.2013.11.003.

As the prevalence of metabolic syndrome and diabetes increases, many patients present with low concentrations of HDL (HDL cholesterol <1.0 mmol/L [<40 mg/dL]). A baseline measurement of HDL cholesterol indubitably correlates with future cardiovascular risk. Yet, the utility of therapies that raise HDL cholesterol levels in blood as effective interventions to reduce cardiovascular vascular events has come into question. Blood HDL levels vary inversely with those of triglycerides, and the independent role of HDL versus triglycerides as a cardiovascular risk factor remains unsettled. The 2013 guideline does not advocate any specific therapy for raising HDL. Indeed, multiple recent trials failed to show that raising HDL cholesterol levels improves cardiovascular outcomes, and recent genetic studies cast doubt on low HDL as a causal risk factor for atherosclerotic events. Weight loss and physical activity can raise HDL, and these lifestyle measures merit universal adoption (Table 36-3). Nicotinic acid, particularly in combination with statins, can robustly raise HDL, but clinical trial data do not support the effectiveness of nicotinic acid in cardiovascular risk reduction. Agonists of nuclear receptors provide another potential avenue for raising HDL

levels. Yet patients treated with peroxisome proliferator-activated receptors alpha and gamma (PPAR- α and - γ) agonists have not consistently shown improved cardiovascular outcomes, and at least some PPAR agonists have been associated with worsened cardiovascular outcomes. Other agents in clinical development raise HDL levels by inhibiting cholesteryl ester transfer protein (CETP). Two such agents have undergone large-scale clinical evaluation and have not shown efficacy in improving cardiovascular outcomes. Clinical studies currently under way will assess the effectiveness of two other CETP inhibitors that lack some of the adverse off-target actions encountered with the first agent tested.

The mechanism by which elevated LDL levels promote atherogenesis may involve oxidative modification. Yet, rigorous and well-controlled clinical trials have failed to demonstrate that antioxidant vitamin therapy improves coronary heart disease (CHD) outcomes. In regard to nontraditional risk factors including homocysteine and infection, large-scale clinical trials using vitamins to lower homocysteine or using antibiotics have not reduced cardiovascular events. Therefore, the current evidence base does not support the use of vitamins or antibiotics to lower cardiovascular risk.

Hypertension

(See also Chap. 43) A wealth of epidemiologic data support a relationship between hypertension and atherosclerotic risk, and extensive clinical trial evidence has established that pharmacologic treatment of hypertension can reduce the risk of stroke, heart failure, and CHD events.

Diabetes mellitus, insulin resistance, and the metabolic syndrome

Most patients with diabetes mellitus die of atherosclerosis and its complications. Aging and rampant obesity underlie a current epidemic of type 2 diabetes mellitus. The abnormal lipoprotein profile associated with insulin resistance, known as diabetic dyslipidemia, accounts for part of the elevated cardiovascular risk in patients with type 2 diabetes. Although diabetic individuals often have LDL cholesterol levels near the average, the LDL particles tend to be smaller and denser and, therefore, more atherogenic. Other features of diabetic dyslipidemia include low HDL and elevated triglyceride levels. Hypertension also frequently accompanies obesity, insulin resistance, and dyslipidemia. This commonly encountered clinical cluster of risk factors has become known as the metabolic syndrome (Chap. 38). Despite legitimate concerns about whether clustered components confer more risk than the individual components, the metabolic syndrome concept may offer clinical utility.

Therapeutic objectives for intervention in these patients include addressing the underlying causes, including obesity and low physical activity, by initiating lifestyle measures (see below). Establishing that strict glycemic control reduces the risk of macrovascular complications of diabetes has proved much more elusive than the beneficial effects on microvascular complications such as retinopathy and renal disease. Indeed, “tight” glycemic control may increase adverse events in patients with type 2 diabetes, lending even greater importance to aggressive control of other aspects of risk in this patient population. In this regard, multiple clinical trials have demonstrated unequivocal benefit of statin therapy in diabetic patients over all ranges of LDL cholesterol levels (but not those with end-stage renal disease or advanced heart failure). Among the oral hypoglycemic agents, metformin possesses the best evidence base for cardiovascular event reduction. The novel oral hypoglycemic agents tested in sufficiently powered trials, the dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin and alogliptin, did not show cardiovascular benefit. Indeed, saxagliptin was associated with a slight increase in heart failure. Diabetic populations appear to derive particular benefit from antihypertensive strategies that block the action of angiotensin II. Thus, the antihypertensive regimen for patients with the metabolic syndrome should include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers when possible. Many of these individuals will require more than one antihypertensive agent to reach the 2013 goals for individuals 18 years of age or older with diabetes to achieve a systolic blood pressure of less than 140 mmHg and a diastolic blood pressure of less than 90 mmHg.

Male sex/postmenopausal state

Decades of observational studies have verified excess coronary risk in men compared with premenopausal women. After menopause, however, coronary risk accelerates in women. Although observational and experimental studies have suggested that estrogen therapy reduces coronary risk, large-scale randomized clinical trials have not demonstrated a net benefit of estrogen with or without progestins on CHD outcomes. In the Heart and Estrogen/Progestin Replacement Study (HERS), postmenopausal female survivors of acute MI were randomized to an estrogen/progestin combination or to placebo. This study showed no overall reduction in recurrent coronary events in the active treatment arm. Indeed, early in the 5-year course of this trial, a trend occurred toward an increase in vascular events in the treated women. Extended follow-up of this cohort did not disclose an accrual of benefit in the treatment group. The Women’s Health Initiative (WHI) study arm, using a similar estrogen plus progesterone

regimen, was halted due to a small but significant hazard of cardiovascular events, stroke, and breast cancer. The estrogen without progestin arm of WHI (conducted in women without a uterus) was stopped early due to an increase in strokes, and failed to afford protection from MI or CHD death during observation over 7 years. The excess cardiovascular events in these trials may result from an increase in thromboembolism. Physicians should work with women to provide information and help weigh the small but evident CHD risk of estrogen $\pm$ progestin versus the benefits for postmenopausal symptoms and osteoporosis, taking personal preferences into account. Post hoc analyses of observational studies suggest that estrogen therapy in women younger than or closer to menopause than the women enrolled in WHI might confer cardiovascular benefit. Thus, the timing in relation to menopause or the age at which estrogen therapy begins may influence its risk/benefit balance.

The lack of efficacy of estrogen therapy in cardiovascular risk reduction highlights the need for redoubled attention to known modifiable risk factors in women. Meta-analysis supports the efficacy of statins to reduce cardiovascular events in women in primary prevention, as well as in those who have already experienced a cardiovascular event.

Dysregulated coagulation or fibrinolysis

Thrombosis ultimately causes the gravest complications of atherosclerosis. The propensity to form thrombi and/or lyse clots once they form influences the manifestations of atherosclerosis. Thrombosis provoked by atheroma rupture and subsequent healing may promote plaque growth. Certain individual characteristics can influence thrombosis or fibrinolysis and have received attention as potential coronary risk factors. For example, fibrinogen levels correlate with coronary risk and provide information about coronary risk independent of the lipoprotein profile.

The stability of an arterial thrombus depends on the balance between fibrinolytic factors, such as plasmin, and inhibitors of the fibrinolytic system, such as plasminogen activator inhibitor 1 (PAI-1). Individuals with diabetes mellitus or the metabolic syndrome have elevated levels of PAI-1 in plasma, and this probably contributes to the increased risk of thrombotic events. Lp(a) (**Chap. 37**) may modulate fibrinolysis, and individuals with elevated Lp(a) levels have increased CHD risk.

Aspirin reduces CHD events in several contexts. **Chapter 39** discusses aspirin therapy in stable ischemic heart disease, and **Chap. 40** reviews recommendations for aspirin treatment in acute coronary syndromes. In primary prevention, pooled trial data show that low-dose aspirin treatment (81 mg/d to 325 mg

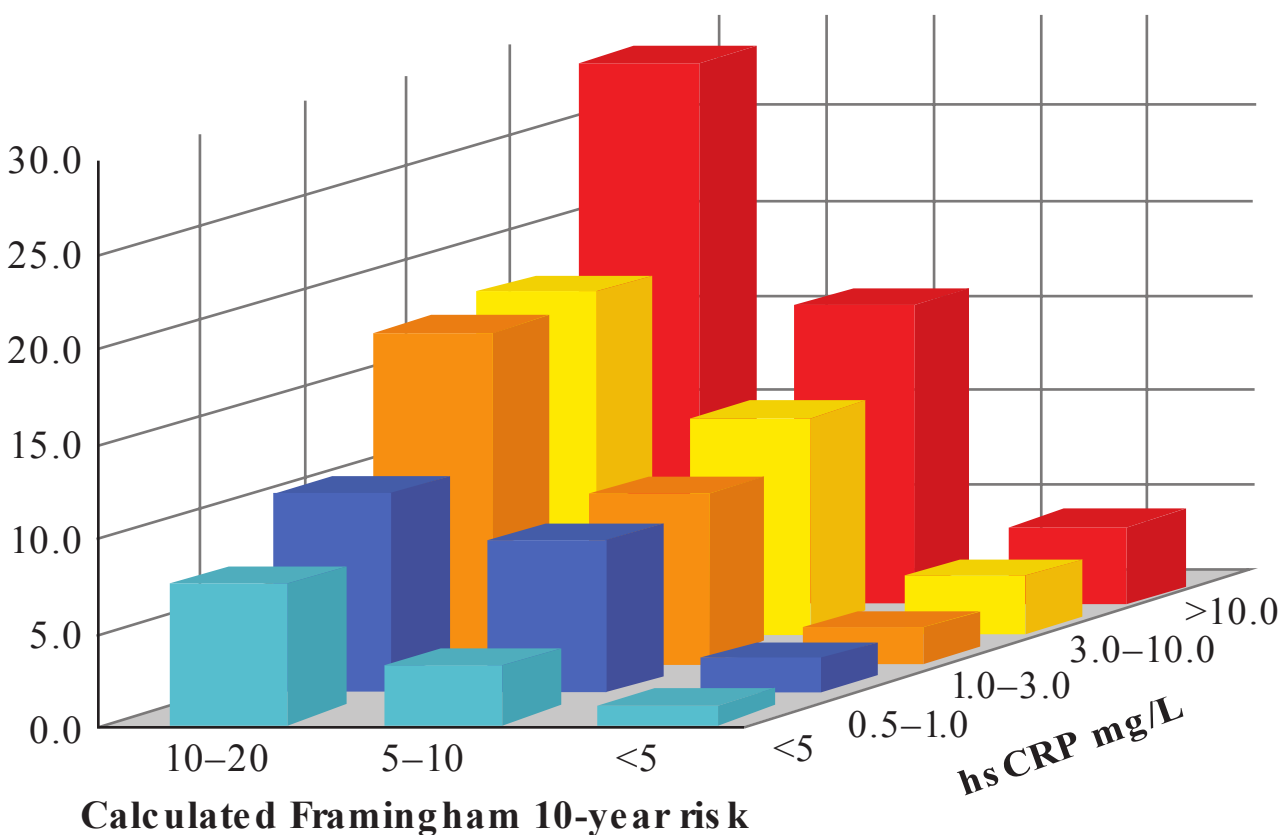


FIGURE 36-6
C-reactive protein (CRP) level adds to the predictive value of the Framingham score. hsCRP, high-sensitivity measurement of CRP. (Adapted from PMRidker et al: *Circulation* 109:2818, 2004.)

on alternate days) can reduce the risk of a first MI in men. Although the Women’s Health Study (WHS) showed that aspirin (100 mg on alternate days) reduced strokes by 17%, it did not prevent MI in women. Current AHA guidelines recommend the use of low-dose aspirin (75–160 mg/d) for women with high cardiovascular risk ($\geq 20\%$ 10-year risk), for men with a $\geq 10\%$ 10-year risk of CHD, and for all aspirin-tolerant patients with established cardiovascular disease who lack contraindications.

Inflammation

An accumulation of clinical evidence shows that markers of inflammation correlate with coronary risk. For example, plasma levels of CRP, as measured by a high-sensitivity assay (hsCRP), prospectively predict the risk of MI. CRP levels also correlate with the outcome in patients with acute coronary syndromes. In contrast to several other novel risk factors, CRP adds predictive information to that derived from established risk factors, such as those included in the Framingham score (**Fig. 36-6**). Mendelian randomization studies do not support a causal role for CRP in cardiovascular disease. Thus, CRP serves as a validated biomarker of risk, but probably not as a direct contributor to pathogenesis.

Elevations in acute-phase reactants such as fibrinogen and CRP reflect the overall inflammatory burden, not just vascular foci of inflammation. Visceral adipose tissue releases proinflammatory cytokines that drive CRP production and may represent a major extravascular stimulus to the elevation of inflammatory markers in obese and overweight individuals. Indeed, CRP levels rise with body mass index (BMI) or visceral adipose depot as assessed by imaging, and weight reduction lowers CRP levels. Infectious agents might also furnish inflammatory stimuli related to cardiovascular risk.

Statin therapy likely reduces cardiovascular events in part by muting the inflammatory aspects of the pathogenesis of atherosclerosis. For example, in statin trials conducted in both primary (JUPITER) and secondary (PROVE-IT/TIMI-22) prevention populations, prespecified analyses showed that those who achieved lower levels of both LDL and CRP had better clinical outcomes than did those who only reached the lower level of either the inflammatory marker or the atherogenic lipoprotein (**Fig. 36-7**). The anti-inflammatory effect of statins appears independent of LDL lowering, because these two variables correlated very poorly in individual subjects in multiple clinical trials.

Group	N	Rate
Placebo	7832	1.11
LDL $\geq$ 70 mg/dL, hsCRP $\geq$ 2 mg/L	1384	1.11
LDL $<$ 70 mg/dL, hsCRP $\geq$ 2 mg/L	2921	0.62
LDL $\geq$ 70 mg/dL, hsCRP $<$ 2 mg/L	726	0.54
LDL $<$ 70 mg/dL, hsCRP $<$ 2 mg/L	2685	0.38

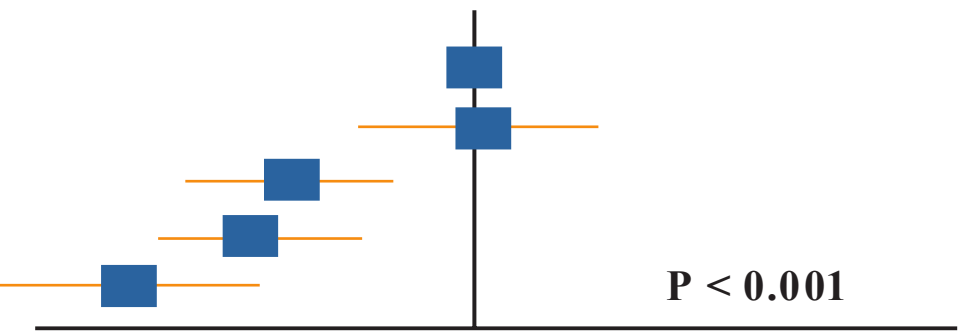


FIGURE 36-7
Evidence from the JUPITER study that both low-density lipoprotein (LDL)-lowering and anti-inflammatory actions contribute to the benefit of statin therapy in primary prevention. See text for explanation. hsCRP, high-sensitivity measurement of C-reactive protein (CRP). (Adapted from PM Ridker et al: *Lancet* 373:1175, 2009.)

Lifestyle modification

The prevention of atherosclerosis presents a long-term challenge to all health care professionals and for public health policy. Both individual practitioners and organizations providing health care should strive to help patients optimize their risk factor profiles long before atherosclerotic disease becomes manifest. The current accumulation of cardiovascular risk in youth and in certain minority populations presents a particularly vexing concern from a public health perspective.

The ACC/AHA 2013 Guideline on Lifestyle Management to Reduce Cardiovascular Risk relied on rigorous evidentiary reviews. Few lifestyle interventions have undergone rigorous evaluation in randomized clinical trials. Therefore, these guidelines reflected judicious analysis of carefully selected observational studies and of intervention studies that relied primarily on biomarkers or surrogate endpoints rather than “hard” cardiovascular outcomes. Table 36-3 summarizes the ACC/AHA lifestyle recommendations.

The care plan for all patients seen by internists should include measures to assess and minimize cardiovascular risk. Physicians must counsel patients about the health risks of tobacco use and provide guidance and resources regarding smoking cessation. Similarly, physicians should advise all patients about prudent dietary and physical activity habits for maintaining ideal body weight. Both National Institutes of Health (NIH) and AHA statements recommend at least 30 min of moderate-intensity physical activity per day. Obesity, particularly the male pattern of centripetal or visceral fat accumulation, can contribute to the elements of the “metabolic syndrome” cluster. Physicians should encourage their patients to take personal responsibility for behavior related to modifiable risk factors for the development of premature atherosclerotic disease. Conscientious counseling and patient education may forestall the need for pharmacologic measures intended to reduce coronary risk.

Issues in risk assessment

A growing panel of markers of coronary risk presents a perplexing array to the practitioner. Markers measured in peripheral blood include size fractions of LDL particles and concentrations of homocysteine, Lp(a), fibrinogen, CRP, PAI-1, myeloperoxidase, lipoprotein-associated phospholipase A₂, and imaging assessment of subclinical atherosclerosis, among many others. In general, such specialized tests add little to the information available from a careful history and physical examination combined with measurement of a plasma lipoprotein profile and fasting blood glucose. The hsCRP

measurement may well prove an exception in view of its robustness in risk prediction, ease of reproducible and standardized measurement, relative stability in individuals over time, ability to add to the risk information disclosed by standard measurements such as the components of the Framingham risk score, and most importantly, the demonstration in a large-scale trial (JUPITER) that allocating therapy can reduce cardiovascular events in those deemed ineligible by traditional risk assessment criteria. The addition of information regarding a family history of premature atherosclerosis (a simply obtained indicator of genetic susceptibility), together with the inflammation marker hsCRP, permits correct reclassification of risk in individuals, especially those whose Framingham scores place them at intermediate risk.

Available data do not support the routine use of imaging studies to screen for subclinical disease (e.g., measurement of carotid intima-media thickness, coronary artery calcification, and use of computed tomographic coronary angiograms [CTA]). Inappropriate use of such imaging modalities may promote excessive alarm in asymptomatic individuals and prompt invasive diagnostic and therapeutic procedures of unproven value for both asymptomatic atherosclerosis and incidental findings. Widespread application of such modalities for screening should await proof that targeting therapies based on their application provides clinical benefit.

The 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk recommends the use of newer risk markers if uncertainty persists after assessing quantitative risk using the pooled cohort calculator. The guideline states that family history, hsCRP, coronary artery calcium (CAC) score, or ankle-brachial index (ABI) may then be considered to inform treatment decision making. It discourages carotid intima-media thickness (CMT) for routine measurement in clinical practice for risk assessment for a first ASCVD event. The guideline panel deemed the contribution to risk assessment for a first ASCVD event using apolipoprotein B (ApoB), chronic kidney disease, albuminuria, or cardiorespiratory fitness as uncertain at present.

Progress in human genetics holds considerable promise for risk prediction and for individualization of cardiovascular therapy. Many early reports identified single-nucleotide polymorphisms (SNPs) in candidate genes as predictors of cardiovascular risk. The validation of such genetic markers of risk and drug responsiveness in multiple populations often proved disappointing. The era of GWAS has led to discovery of sites of genetic variation that reproducibly indicate heightened cardiovascular risk (e.g., chromosome 9p21). The advent of technology that permits relatively rapid and inexpensive exome or whole-genome

sequencing promises to identify new therapeutic targets, sharpen risk prediction, and deploy preventive or therapeutic measures in a more personalized manner. Despite this considerable promise, genetic scores for risk prediction have not yet demonstrated consistent improvement over algorithms that use traditional tools.

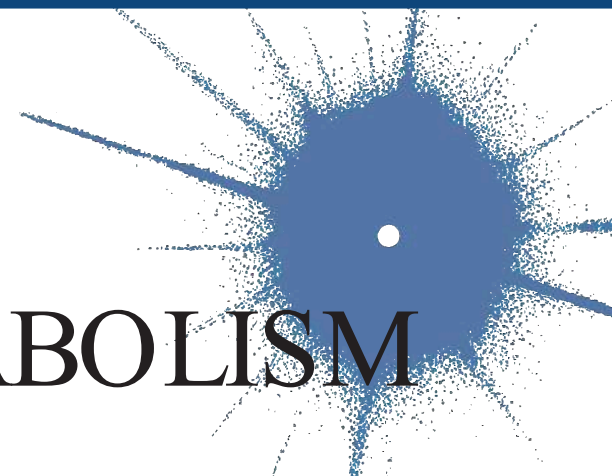
THE CHALLENGE OF IMPLEMENTATION: CHANGING PHYSICIAN AND PATIENT BEHAVIOR

Despite declining age-adjusted rates of coronary death, cardiovascular mortality worldwide is rising due to aging of the population and due to subsiding of communicable diseases and increased prevalence of risk

factors in developing countries. Enormous challenges remain regarding translation of the current evidence base into practice. Physicians must learn how to help individuals adopt a healthy lifestyle in a culturally appropriate manner and to deploy their increasingly powerful pharmacologic tools most economically and effectively. The obstacles to implementation of current evidence-based prevention and treatment of atherosclerosis involve economics, education, physician awareness, and patient adherence to recommended regimens. Future goals in the treatment of atherosclerosis should include more widespread implementation of the current evidence-based guidelines regarding risk factor management and, when appropriate, drug therapy.

CHAPTER 37

DISORDERS OF LIPOPROTEIN METABOLISM



Daniel J. Rader ■ Helen H. Hobbs

Lipoproteins are complexes of lipids and proteins that are essential for transport of cholesterol, triglycerides, and fat-soluble vitamins. Previously, lipoprotein disorders were the purview of specialized lipidologists, but the demonstration that lipid-lowering therapy significantly reduces the clinical complications of atherosclerotic cardiovascular disease (ASCVD) has brought the diagnosis and treatment of these disorders into the domain of the internist. The number of individuals who are candidates for lipid-lowering therapy continues to increase. Therefore, the appropriate diagnosis and management of lipoprotein disorders is of critical importance in the practice of medicine. This chapter reviews normal lipoprotein physiology, the pathophysiology of disorders of lipoprotein metabolism, the effects of diet and other environmental factors that influence lipoprotein metabolism, and the practical approaches to the diagnosis and management of lipoprotein disorders.

LIPOPROTEIN METABOLISM

LIPOPROTEIN CLASSIFICATION AND COMPOSITION

Lipoproteins are large macromolecular complexes composed of lipids and proteins that transport poorly soluble lipids (primarily triglycerides, cholesterol, and fat-soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to and from tissues. Lipoproteins play an essential role in the absorption of dietary cholesterol, long-chain fatty acids, and fat-soluble vitamins; the transport of triglycerides, cholesterol, and fat-soluble vitamins from the liver to peripheral tissues; and the transport of cholesterol from peripheral tissues to the liver and intestine.

Lipoproteins contain a core of hydrophobic lipids (triglycerides and cholesteryl esters) surrounded by a shell of hydrophilic lipids (phospholipids, unesterified

cholesterol) and proteins (called apolipoproteins) that interact with body fluids. The plasma lipoproteins are divided into five major classes based on their relative density (**Fig. 37-1** and **Table 37-1**): chylomicrons, very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs). Each lipoprotein class comprises a family of particles that vary in density, size, and protein composition. Because lipid is less dense than water, the density of a lipoprotein particle is primarily determined by the amount of lipid per particle. Chylomicrons are the most lipid-rich and therefore least dense lipoprotein particles, whereas HDLs have the least lipid and are therefore the most dense lipoproteins. In addition to their density, lipoprotein particles can be classified according to their size, determined either by nondenaturing gel electrophoresis or by nuclear magnetic resonance profiling. There is a strong inverse relationship between density and size, with the largest particles being the most buoyant (chylomicrons) and the smallest particles being the most dense (HDL).

The proteins associated with lipoproteins, called apolipoproteins (**Table 37-2**), are required for the assembly, structure, function, and metabolism of lipoproteins. Apolipoproteins activate enzymes important in lipoprotein metabolism and act as ligands for cell surface receptors. ApoB is a very large protein and is the major structural protein of chylomicrons, VLDLs, IDLs, and LDLs; one molecule of apoB, either apoB-48 (chylomicron) or apoB-100 (VLDL, IDL, or LDL), is present on each lipoprotein particle. The human liver synthesizes apoB-100, and the intestine makes apoB-48, which is derived from the same gene by mRNA editing. HDLs have different apolipoproteins that define this lipoprotein class, most importantly apoA-I, which is synthesized in the liver and intestine and is found on virtually all HDL particles. ApoA-II is the second most abundant HDL

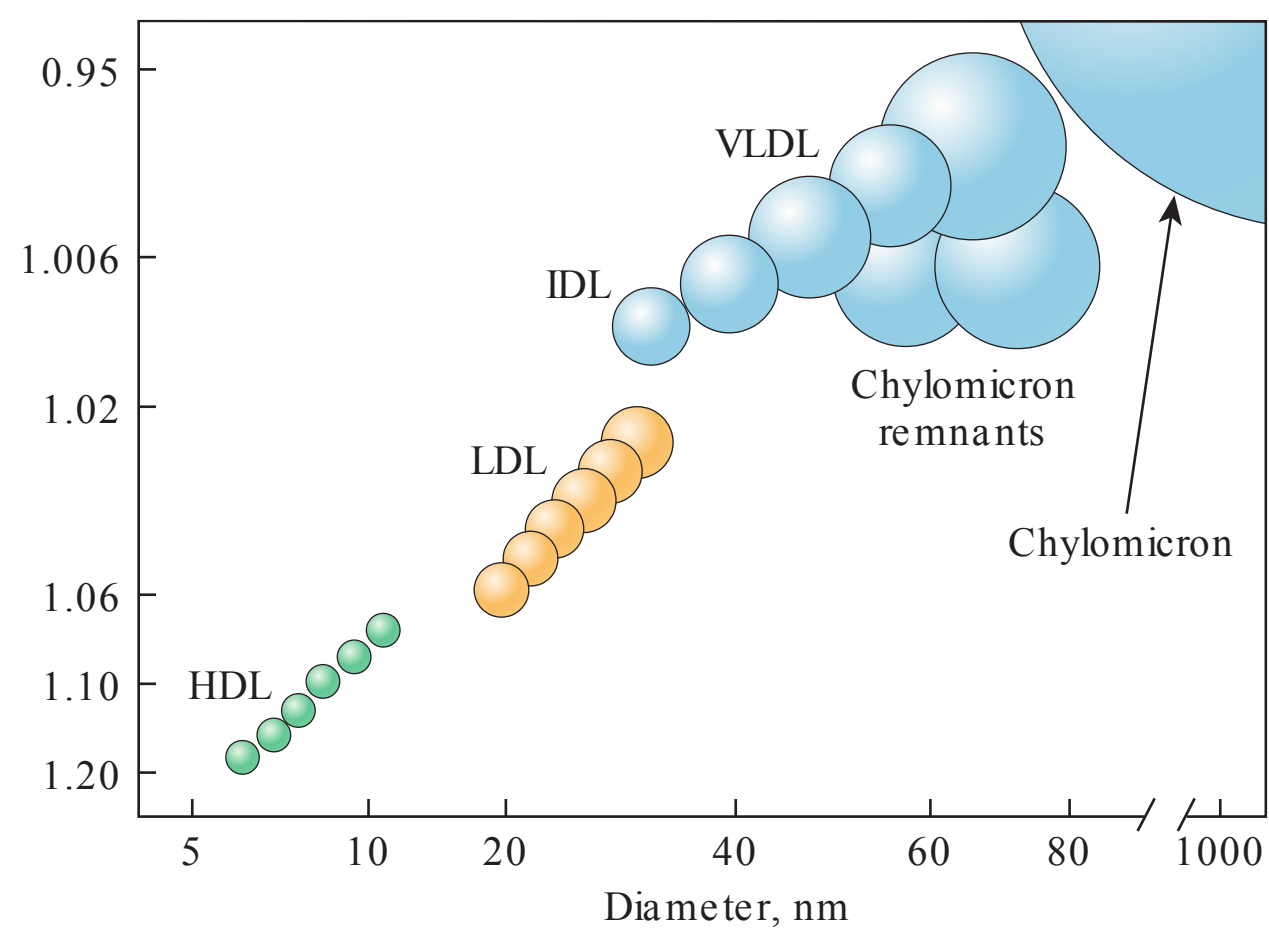


FIGURE 37-1
The density and size distribution of the major classes of lipoprotein particles. Lipoproteins are classified by density and size, which are inversely related. HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

apolipoprotein and is on approximately two-thirds of the HDL particles. ApoC-I, apoC-II, and apoC-III participate in the metabolism of triglyceride-rich lipoproteins. ApoE also plays a critical role in the metabolism and clearance of triglyceride-rich particles. Most apolipoproteins, other than apoB, exchange actively among lipoprotein particles in the blood.

Apolipoprotein(a) [apo(a)] is a distinctive apolipoprotein and is discussed more below.

TRANSPORT OF INTESTINALLY DERIVED DIETARY LIPIDS BY CHYLOMICRONS

One critical role of lipoproteins is the efficient transport of dietary lipids from the intestine to tissues that require fatty acids for energy or store and metabolize lipids (Fig. 37-2). Dietary triglycerides are hydrolyzed by lipases within the intestinal lumen and emulsified with bile acids to form micelles. Dietary cholesterol, fatty acids, and fat-soluble vitamins are absorbed in the proximal small intestine. Cholesterol and retinol are esterified (by the addition of a fatty acid) in the enterocyte to form cholesteryl esters and retinyl esters, respectively. Longer-chain fatty acids (>12 carbons) are incorporated into triglycerides and packaged with apoB-48, cholesteryl esters, retinyl esters, phospholipids, and cholesterol to form chylomicrons. Nascent chylomicrons are secreted into the intestinal lymph and delivered via the thoracic duct directly to the systemic circulation, where they are extensively processed by peripheral tissues before reaching the liver. The particles encounter lipoprotein lipase (LPL), which is anchored to a glycosylphosphatidylinositol-anchored protein, GPIHBP1, that is attached to the endothelial surfaces of capillaries in adipose tissue, heart, and skeletal muscle (Fig. 37-2). The triglycerides

TABLE 37-1
MAJOR LIPOPROTEIN CLASSES

LIPOPROTEIN	DENSITY, G/mL ^a	SIZE, nm ^b	ELECTROPHORETIC MOBILITY ^c	APOLIPOPROTEINS		
				MAJOR	OTHER	OTHER CONSTITUENTS
Chylomicrons	0.930	75–1200	Origin	ApoB-48	A-I, A-V, C-I, C-II, C-III, E	Retinyl esters
Chylomicron remnants	0.930–1.006	30–80	Slow pre-β	ApoB-48	A-I, A-V, C-I, C-II, C-III, E	Retinyl esters
VLDL	0.930–1.006	30–80	Pre-β	ApoB-100	A-I, A-II, A-V, C-I, C-II, C-III, E	Vitamin E
IDL	1.006–1.019	25–35	Slow pre-β	ApoB-100	C-I, C-II, C-III, E	Vitamin E
LDL	1.019–1.063	18–25	β	ApoB-100		Vitamin E
HDL	1.063–1.210	5–12	α	ApoA-I	A-II, A-IV, A-V, C-III, E	LCAT, CETP, paroxonase
Lp(a)	1.050–1.120	25	Pre-β	ApoB-100	Apo(a)	Oxidized phospholipids

^aThe density of the particle is determined by ultracentrifugation.
^bThe size of the particle is measured using gel electrophoresis.
^cThe electrophoretic mobility of the particle on agarose gel electrophoresis reflects the size and surface charge of the particle, with β being the position of LDL and α being the position of HDL.
Note: All of the lipoprotein classes contain phospholipids, esterified and unesterified cholesterol, and triglycerides to varying degrees.
Abbreviations: CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein A; VLDL, very-low-density lipoprotein.

TABLE 37-2

MAJOR APOLIPOPROTEINS			
APOLIPOPROTEIN	PRIMARY SOURCE	LIPOPROTEIN ASSOCIATION	FUNCTION
ApoA-I	Intestine, liver	HDL, chylomicrons	Structural protein for HDL Activates LCAT
ApoA-II	Liver	HDL, chylomicrons	Structural protein for HDL
ApoA-IV	Intestine, liver	HDL, chylomicrons	Unknown
ApoA-V	Liver	VLDL, chylomicrons	Promotes LPL-mediated triglyceride lipolysis
Apo(a)	Liver	Lp(a)	Unknown
ApoB-48	Intestine	Chylomicrons, chylomicron remnants	Structural protein for chylomicrons
ApoB-100	Liver	VLDL, IDL, LDL, Lp(a)	Structural protein for VLDL, IDL, LDL, Lp(a) Ligand for binding to LDL receptor
ApoC-I	Liver	Chylomicrons, VLDL, HDL	Unknown
ApoC-II	Liver	Chylomicrons, VLDL, HDL	Cofactor for LPL
ApoC-III	Liver, intestine	Chylomicrons, VLDL, HDL	Inhibits LPL activity and lipoprotein binding to receptors
ApoE	Liver	Chylomicron remnants, IDL, HDL	Ligand for binding to LDL receptor and other receptors

Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein A; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

of chylomicrons are hydrolyzed by LPL, and free fatty acids are released. ApoC-II, which is transferred to circulating chylomicrons from HDL, acts as a required cofactor for LPL in this reaction. The released free fatty acids are taken up by adjacent myocytes or adipocytes and either oxidized to generate energy or reesterified and stored as triglyceride. Some of the released free fatty acids bind albumin before entering cells and are transported to other tissues, especially the liver. The chylomicron particle progressively shrinks in size as the hydrophobic core is hydrolyzed and the hydrophilic lipids (cholesterol and phospholipids) and apolipoproteins on the particle surface are transferred to HDL, creating chylomicron remnants.

Chylomicron remnants are rapidly removed from the circulation by the liver through a process that requires apoE as a ligand for receptors in the liver. Consequently, few, if any, chylomicrons or chylomicron remnants are generally present in the blood after a 12-h fast, except in patients with certain disorders of lipoprotein metabolism.

TRANSPORT OF HEPATICALLY DERIVED LIPIDS BY VLDL AND LDL

Another key role of lipoproteins is the transport of hepatic lipids from the liver to the periphery (Fig. 37-2). VLDL particles resemble chylomicrons in

protein composition but contain apoB-100 rather than apoB-48 and have a higher ratio of cholesterol to triglyceride (~1 mg of cholesterol for every 5 mg of triglyceride). The triglycerides of VLDL are derived predominantly from the esterification of long-chain fatty acids in the liver. The packaging of hepatic triglycerides with the other major components of the nascent VLDL particle (apoB-100, cholesteryl esters, phospholipids, and vitamin E) requires the action of the enzyme microsomal triglyceride transfer protein (MTP). After secretion into the plasma, VLDL acquires multiple copies of apoE and apolipoproteins of the C series by transfer from HDL. As with chylomicrons, the triglycerides of VLDL are hydrolyzed by LPL, especially in muscle, heart, and adipose tissue. After the VLDL remnants dissociate from LPL, they are referred to as IDLs, which contain roughly similar amounts of cholesterol and triglyceride. The liver removes approximately 40–60% of IDL by LDL receptor-mediated endocytosis via binding to apoE. The remainder of IDL is remodeled by hepatic lipase (HL) to form LDL. During this process, phospholipids and triglyceride in the particle are hydrolyzed, and all apolipoproteins except apoB-100 are transferred to other lipoproteins. Approximately 70% of LDL is removed from the circulation by the liver in a similar manner as IDL; however, in this case, apoB, rather than apoE, binds the LDL receptor.

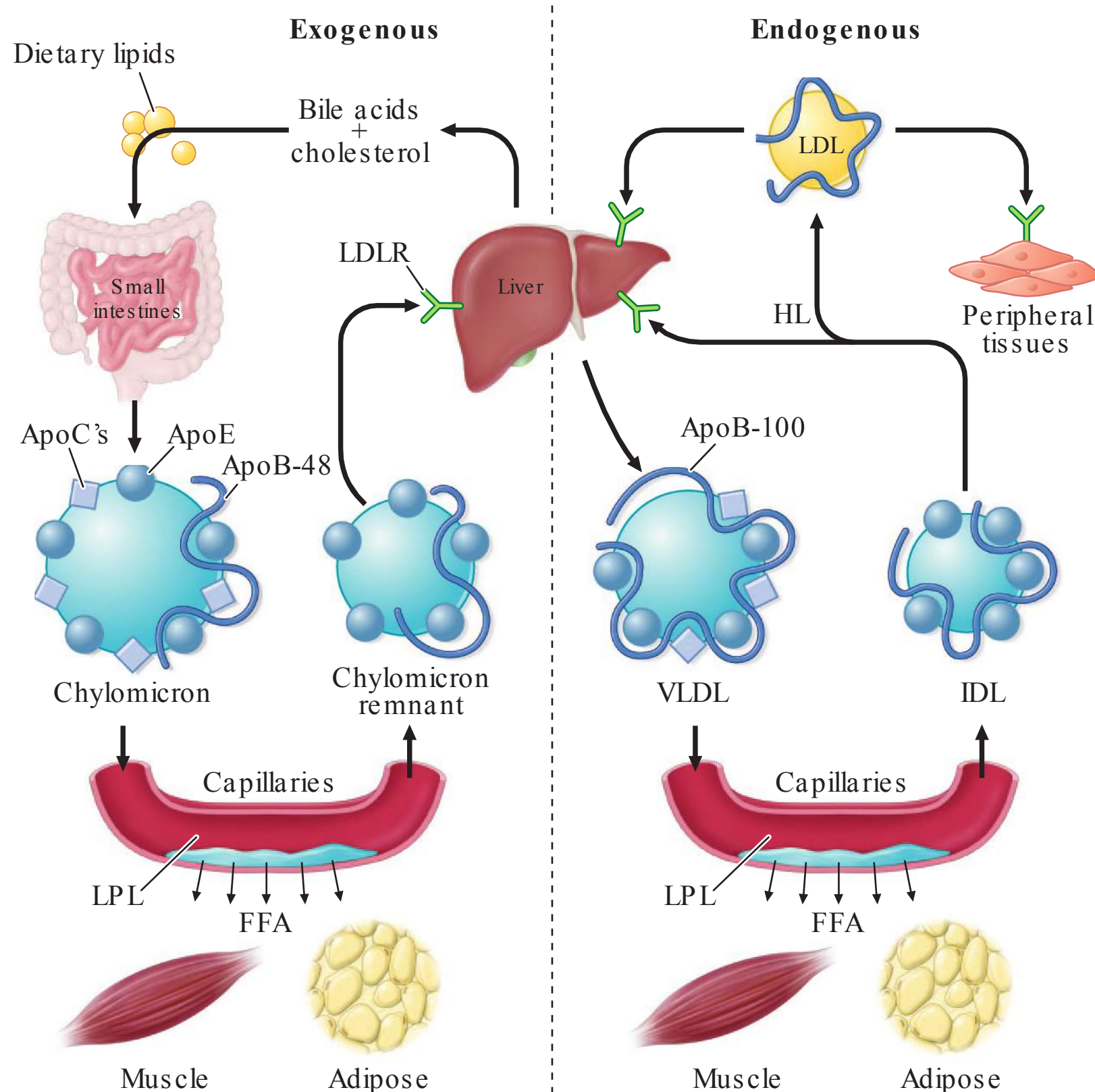


FIGURE 37-2

The exogenous and endogenous lipoprotein metabolic pathways. The exogenous pathway transports dietary lipids to the periphery and the liver. The endogenous pathway transports hepatic lipids to the periphery. FFA, free fatty acid; HL, hepatic

lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

Lp(a) is a lipoprotein similar to LDL in lipid and protein composition, but it contains an additional protein called apolipoprotein(a) [apo(a)]. Apo(a) is synthesized in the liver and attached to apoB-100 by a disulfide linkage. The major site of clearance of Lp(a) is the liver, but the uptake pathway is not known.

HDL METABOLISM AND REVERSE CHOLESTEROL TRANSPORT

All nucleated cells synthesize cholesterol, but only hepatocytes and enterocytes can effectively excrete cholesterol from the body, into either the bile or the gut lumen. In the liver, cholesterol is secreted into the bile, either directly or after conversion to bile acids. Cholesterol in peripheral cells is transported from the plasma membranes of peripheral cells to the liver and intestine by a process termed “reverse cholesterol transport” that is facilitated by HDL (Fig. 37-3).

Nascent HDL particles are synthesized by the intestine and the liver. Newly secreted apoA-I rapidly acquires phospholipids and unesterified cholesterol from its site of synthesis (intestine or liver) via a process promoted by the membrane protein ATP-binding

cassette protein A1 (ABCA1). This process results in the formation of discoidal HDL particles, which then recruit additional unesterified cholesterol from cells or circulating lipoproteins. Within the HDL particle, the cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT), a plasma enzyme associated with HDL, and the more hydrophobic cholesteryl ester moves to the core of the HDL particle. As HDL acquires more cholesteryl ester, it becomes spherical, and additional apolipoproteins and lipids are transferred to the particles from the surfaces of chylomicrons and VLDLs during lipolysis.

HDL cholesterol is transported to hepatocytes by both an indirect and a direct pathway. HDL cholesteryl esters can be transferred to apoB-containing lipoproteins in exchange for triglyceride by the cholesteryl ester transfer protein (CETP). The cholesteryl esters are then removed from the circulation by LDL receptor-mediated endocytosis. HDL cholesterol can also be taken up directly by hepatocytes via the scavenger receptor class B1 (SR-B1), a cell surface receptor that mediates the selective transfer of lipids to cells.

HDL particles undergo extensive remodeling within the plasma compartment by a variety of lipid transfer proteins

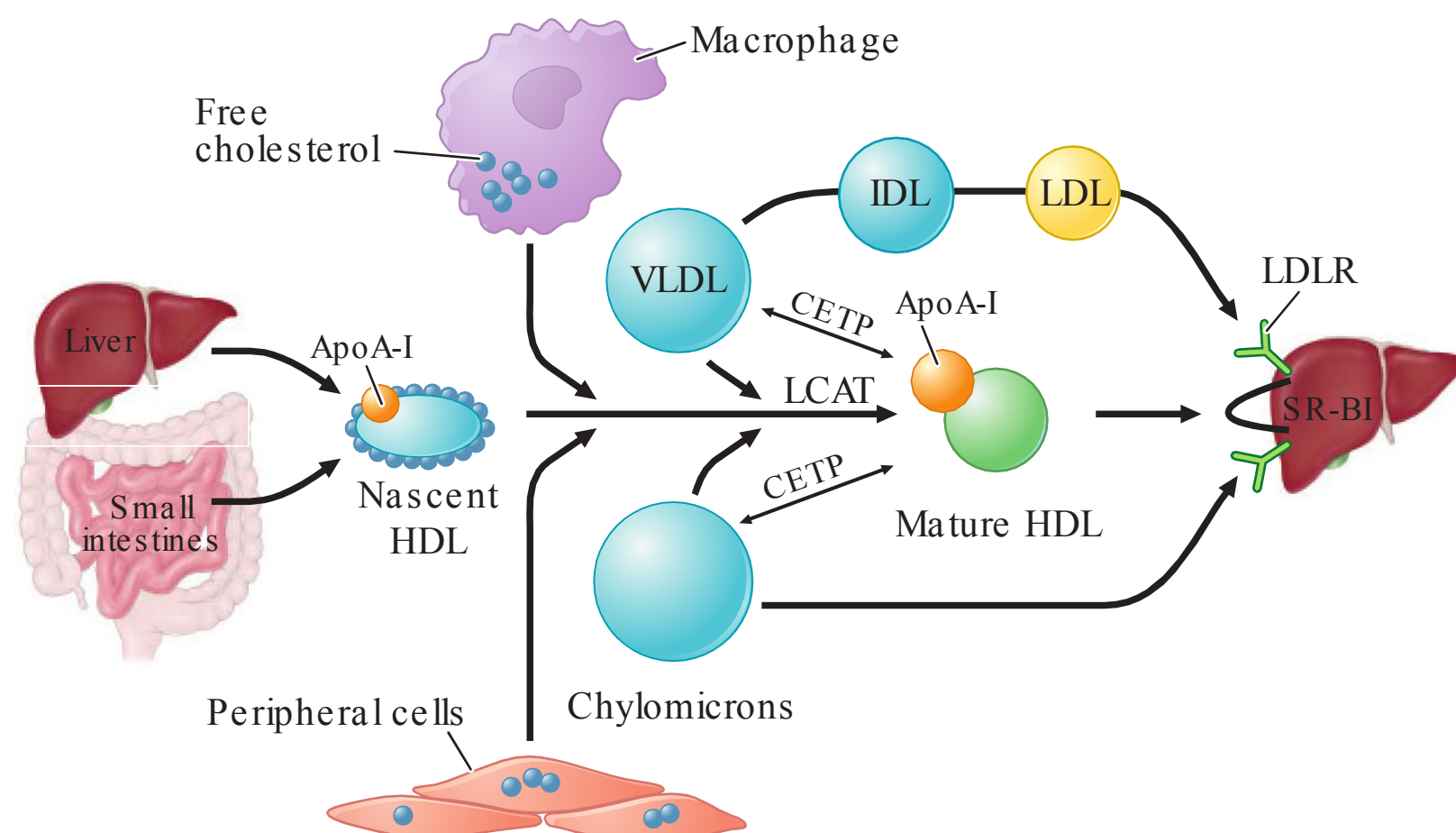


FIGURE 37-3

High-density lipoprotein (HDL) metabolism and reverse cholesterol transport. This pathway transports excess cholesterol from the periphery back to the liver for excretion in the bile. The liver and the intestine produce nascent HDLs. Free cholesterol is acquired from macrophages and other peripheral cells and esterified by lecithin-cholesterol acyltransferase (LCAT), forming mature HDLs. HDL cholesterol can be selectively taken up by

the liver via SR-BI (scavenger receptor class BI). Alternatively, HDL cholesteryl ester can be transferred by cholesteryl ester transfer protein (CETP) from HDLs to very-low-density lipoproteins (VLDLs) and chylomicrons, which can then be taken up by the liver. IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor.

and lipases. The phospholipid transfer protein (PLTP) transfers phospholipids from other lipoproteins to HDL or among different classes of HDL particles. After CETP- and PLTP-mediated lipid exchange, the triglyceride-enriched HDL becomes a much better substrate for HL, which hydrolyzes the triglycerides and phospholipids to generate smaller HDL particles. A related enzyme called endothelial lipase hydrolyzes HDL phospholipids, generating smaller HDL particles that are catabolized faster. Remodeling of HDL influences the metabolism, function, and plasma concentrations of HDL.

DISORDERS OF ELEVATED CHOLESTEROL AND TRIGLYCERIDES

Disorders of lipoprotein metabolism are collectively referred to as “dyslipidemias.” Dyslipidemias are generally characterized clinically by increased plasma levels of cholesterol, triglycerides, or both, variably accompanied by reduced levels of HDL cholesterol. Because plasma lipids are commonly screened (see below), dyslipidemia is frequently seen in clinical practice. The majority of patients with dyslipidemia have some combination of genetic predisposition (often polygenic) and environmental contribution (lifestyle, medical condition, or drug). Many, but not all, patients with dyslipidemia are at increased risk for ASCVD, the primary reason for making the diagnosis, as intervention may reduce this risk. In addition, patients with substantially elevated levels of triglycerides may be at risk for acute pancreatitis and require intervention to reduce this risk.

Although literally hundreds of proteins influence lipoprotein metabolism and may interact to produce dyslipidemia in an individual patient, there are a limited number of discrete “nodes” that regulate lipoprotein metabolism. These include: (1) assembly and secretion of triglyceride-rich VLDLs by the liver; (2) lipolysis of triglyceride-rich lipoproteins by LPL; (3) receptor-mediated uptake of apoB-containing lipoproteins by the liver; (4) cellular cholesterol metabolism in the hepatocyte and the enterocyte; and (5) neutral lipid transfer and phospholipid hydrolysis in the plasma. The following discussion will focus on these regulatory nodes, recognizing that in many cases these nodes interact with and influence each other.

DYSLIPIDEMIA CAUSED BY EXCESSIVE HEPATIC SECRETION OF VLDL

Excessive production of VLDL by the liver is one of the most common causes of dyslipidemia. Individuals with excessive hepatic VLDL production usually have elevated fasting triglycerides and low levels of HDL cholesterol (HDL-C), with variable elevations in LDL cholesterol (LDL-C) but usually elevated plasma levels of apoB. A cluster of other metabolic risk factors are often found in association with VLDL overproduction, including obesity, glucose intolerance, insulin resistance, and hypertension (the so-called metabolic syndrome, **Chap. 38**). Some of the major factors that drive hepatic VLDL secretion include obesity, insulin resistance, a high-carbohydrate diet, alcohol use, exogenous estrogens, and genetic predisposition.

Secondary causes of VLDL overproduction

High-carbohydrate diet

Dietary carbohydrates are converted to fatty acids in the liver. Some of the newly synthesized fatty acids are esterified forming triglycerides (TGs) and secreted as constituents of VLDL. Thus, excessive intake of calories as carbohydrates, which is frequent in Western societies, leads to increased hepatic VLDL-TG secretion.

Alcohol

Regular alcohol consumption inhibits hepatic oxidation of free fatty acids, thus promoting hepatic TG synthesis and VLDL secretion. Regular alcohol use also raises plasma levels of HDL-C and should be considered in patients with the unusual combination of elevated TGs and elevated HDL-C.

Obesity and insulin resistance

Obesity and insulin resistance are frequently accompanied by dyslipidemia characterized by elevated plasma levels of TG, low HDL-C, variable levels of LDL-C, and increased levels of small dense LDL. The increase in adipocyte mass and accompanying decreased insulin sensitivity associated with obesity have multiple effects on lipid metabolism, with one of the major effects being excessive hepatic VLDL production. More free fatty acids are delivered from the expanded and insulin-resistant adipose tissue to the liver, where they are reesterified in hepatocytes to form TGs, which are packaged into VLDLs for secretion into the circulation. In addition, the increased insulin levels promote increased fatty acid synthesis in the liver. In insulin-resistant patients who progress to type 2 diabetes mellitus, dyslipidemia remains common, even when the patient is under relatively good glycemic control. In addition to increased VLDL production, insulin resistance can also result in decreased LPL activity, resulting in reduced catabolism of chylomicrons and VLDLs and more severe hypertriglyceridemia (see below).

Nephrotic syndrome

Nephrotic syndrome is a classic cause of excessive VLDL production. The molecular mechanism of VLDL overproduction remains poorly understood but has been attributed to the effects of hypoalbuminemia leading to increased hepatic protein synthesis. Effective treatment of the underlying renal disease often normalizes the lipid profile, but most patients with chronic nephrotic syndrome require lipid-lowering drug therapy.

Cushing's syndrome

Endogenous or exogenous glucocorticoid excess is associated with increased VLDL synthesis and secretion and hypertriglyceridemia. Patients with Cushing's syndrome frequently have dyslipidemia especially

characterized by hypertriglyceridemia and low HDL-C, although elevations in plasma levels of LDL-C can also be seen.

Primary (genetic) causes of VLDL overproduction

Genetic variation influences hepatic VLDL production. A number of genes have been identified in which common and low-frequency variants likely contribute to increased VLDL production, likely involving interactions with diet and other environmental factors. The best recognized inherited condition associated with VLDL overproduction is familial combined hyperlipidemia.

Familial combined hyperlipidemia (FCHL)

FCHL is generally characterized by elevations in plasma levels of TGs (VLDL) and LDL-C (including small dense LDL) and reduced plasma levels of HDL-C. It is estimated to occur in approximately 1 in 100–200 individuals and is an important cause of premature coronary heart disease (CHD); approximately 20% of patients who develop CHD under age 60 have FCHL. FCHL can manifest in childhood but is usually not fully expressed until adulthood. The disease clusters in families, with affected family members typically have one of three possible phenotypes: (1) elevated plasma levels of LDL-C, (2) elevated plasma levels of TGs due to elevation in VLDL, or (3) elevated plasma levels of both LDL-C and TG. The lipoprotein profile can switch among these three phenotypes in the same individual over time and may depend on factors such as diet, exercise, weight, and insulin sensitivity. Patients with FCHL almost always have significantly elevated plasma levels of apoB. The levels of apoB are disproportionately high relative to the plasma LDL-C concentration, indicating the presence of small, dense LDL particles, which are characteristic of this syndrome.

Individuals with this phenotype generally share the same metabolic defect, namely overproduction of VLDL by the liver. The molecular etiology of this condition remains poorly understood, and no single gene has been identified in which mutations cause this disorder. It is likely that defects in a combination of genes can cause the condition, suggesting that a more appropriate term for the disorder might be polygenic combined hyperlipidemia.

The presence of a mixed dyslipidemia (plasma TG levels between 200 and 600 mg/dL and total cholesterol levels between 200 and 400 mg/dL, usually with HDL-C levels <40 mg/dL in men and <50 mg/dL in women) and a family history of mixed dyslipidemia and/or premature CHD strongly suggests the diagnosis. Individuals with this phenotype should be treated aggressively due to significantly increased risk of premature CHD. Decreased dietary intake of simple carbohydrates,

aerobic exercise, and weight loss can all have beneficial effects on the lipid profile. Patients with diabetes should be aggressively treated to maintain good glucose control. Most patients with FCHL require lipid-lowering drug therapy, starting with statins, to reduce lipoprotein levels and lower the risk of cardiovascular disease.

■ Lipodystrophy

Lipodystrophy is a condition in which the generation of adipose tissue generally or in certain fat depots is impaired. Lipodystrophies are often associated with insulin resistance and elevated plasma levels of VLDL and chylomicrons due to increased fatty acid synthesis and VLDL production, as well as reduced clearance of TG-rich particles. This disorder can be especially difficult to control. Patients with congenital generalized lipodystrophy are very rare and have nearly complete absence of subcutaneous fat, accompanied by profound insulin resistance and leptin deficiency, and accumulation of TGs in multiple tissues including the liver. Some patients with generalized lipodystrophy have been treated successfully with leptin administration. Partial lipodystrophy is somewhat more common and can be caused by mutations in several different genes, most notably lamin A. Partial lipodystrophy is usually characterized by increased truncal fat accompanied by markedly reduced or absent subcutaneous fat in the extremities and buttocks. These patients generally have insulin resistance, often quite severe, accompanied by type 2 diabetes, hepatosteatosis, and dyslipidemia. The dyslipidemia is usually characterized by elevated TGs and cholesterol and can be difficult to manage clinically. Patients with partial lipodystrophy are at substantially increased risk of atherosclerotic vascular disease and should therefore be treated aggressively for their dyslipidemia with statins and, if necessary, additional lipid-lowering therapies.

DYSLIPIDEMIA CAUSED BY IMPAIRED LIPOLYSIS OF TRIGLYCERIDE-RICH LIPOPROTEINS

Impaired lipolysis of the TGs in TG-rich lipoproteins (TRLs) also commonly contributes to dyslipidemia. As noted above, LPL is the key enzyme responsible for hydrolyzing the TGs in chylomicrons and VLDL. LPL is synthesized and secreted into the extracellular space from adipocytes, myocytes, and cardiomyocytes. It is then transported from the subendothelial to the vascular endothelial surfaces by GPIHBP1. LPL is also synthesized in macrophages. Individuals with impaired LPL activity, whether secondary or due to a primary genetic disorder, have elevated fasting TGs and low levels of HDL-C, usually without elevation in LDL-C or apoB. Insulin resistance, in addition to causing excessive VLDL production, can also cause impaired

LPL activity and lipolysis. A number of common and low-frequency genetic variants have been described that influence LPL activity, and single-gene Mendelian disorders that reduce LPL activity have also been described (**Table 37-3**).

Secondary causes of impaired lipolysis of TRLs

■ Obesity and insulin resistance

In addition to hepatic overproduction of VLDL, as discussed above, obesity, insulin resistance, and type 2 diabetes have been reported to be associated with variably reduced LPL activity. This may be due in part to the effects of tissue insulin resistance leading to reduced transcription of LPL in skeletal muscle and adipose, as well as to increased production of the LPL inhibitor apoC-III by the liver. This reduction in LPL activity often contributes to the dyslipidemia seen in these patients.

Primary (genetic) causes and genetic predisposition to impaired lipolysis of TRLs

■ Familial chylomicronemia syndrome

As noted above, LPL is required for the hydrolysis of TGs in chylomicrons and VLDLs, and apoC-II is a cofactor for LPL. Genetic deficiency or inactivity of either protein results in impaired lipolysis and profound elevations in plasma chylomicrons. These patients can also have elevated plasma levels of VLDL, but chylomicronemia predominates. The fasting plasma is turbid, and if left at 4°C (39.2°F) for a few hours, the chylomicrons float to the top and form a creamy supernatant. In these disorders, collectively called the familial chylomicronemia syndrome, fasting TG levels are almost invariably >1000 mg/dL. Fasting cholesterol levels are also elevated but to a lesser degree.

LPL deficiency has autosomal recessive inheritance and has a frequency of approximately 1 in 1 million in the population. ApoC-II deficiency is also recessive in inheritance pattern and is even less common than LPL deficiency. Multiple different mutations in the LPL and APOC2 genes cause these diseases. Obligate LPL heterozygotes often have mild-to-moderate elevations in plasma TG levels, whereas individuals heterozygous for mutation in apoC-II do not have hypertriglyceridemia.

Both LPL and apoC-II deficiency usually present in childhood with recurrent episodes of severe abdominal pain due to acute pancreatitis. On fundoscopic examination, the retinal blood vessels are opalescent (lipemia retinalis). Eruptive xanthomas, which are small, yellowish-white papules, often appear in clusters on the back, buttocks, and extensor surfaces of the arms and legs. These typically painless skin lesions may become pruritic. Hepatosplenomegaly results from the uptake of circulating chylomicrons

TABLE 37-3

PRIMARY HYPERLIPOPROTEINEMIAS CAUSED BY KNOWN SINGLE-GENE MUTATIONS					
GENETIC DISORDER	PROTEIN (GENE) DEFECT	LIPOPROTEINS ELEVATED	CLINICAL FINDINGS	GENETIC TRANSMISSION	ESTIMATED INCIDENCE
Hypertriglyceridemia					
Lipoprotein lipase deficiency	LPL (LPL)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	~1/1,000,000
Familial apoC-II deficiency	ApoC-II (APOC2)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
ApoA-V deficiency	ApoA-V (APOA5)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
GPIHBP1 deficiency	GPIHBP1	Chylomicrons	Eruptive xanthomas, pancreatitis	AR	<1/1,000,000
Combined Hyperlipidemia					
Familial hepatic lipase deficiency	Hepatic lipase (LIPC)	VLDL remnants, HDL	Pancreatitis, CHD	AR	<1/1,000,000
Familial dysbetalipoproteinemia	ApoE (APOE)	Chylomicron remnants, VLDL remnants	Palmar and tuberoeruptive xanthomas, CHD, PVD	AR	~1/10,000
Hypercholesterolemia					
Familial hypercholesterolemia	LDL receptor (LDLR)	LDL	Tendon xanthomas, CHD	AD	~1/250 to 1/500
Familial defective apoB-100	ApoB-100 (APOB)	LDL	Tendon xanthomas, CHD	AD	<~1/1500
Autosomal dominant hypercholesterolemia, type 3	PCSK9 (PCSK9)	LDL	Tendon xanthomas, CHD	AD	<1/1,000,000
Autosomal recessive hypercholesterolemia	ARH (LDLRAP)	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000
Sitosterolemia	ABCG5 or ABCG8	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000

Abbreviations: AD, autosomal dominant; apo, apolipoprotein; AR, autosomal recessive; ARH, autosomal recessive hypercholesterolemia; CHD, coronary heart disease; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PVD, peripheral vascular disease; VLDL, very-low density lipoprotein.

by reticuloendothelial cells in the liver and spleen. For unknown reasons, some patients with persistent and pronounced chylomicronemia never develop pancreatitis, eruptive xanthomas, or hepatosplenomegaly. Premature CHD is not generally a feature of familial chylomicronemia syndromes.

The diagnoses of LPL and apoC-II deficiency are established enzymatically in specialized laboratories by assaying TG lipolytic activity in postheparin plasma. Blood is sampled after an IV heparin injection to release the endothelial-bound LPL. LPL activity is profoundly reduced in both LPL and apoC-II deficiency; in patients with apoC-II deficiency, it normalizes after the addition of normal plasma (providing a source of

apoC-II). Molecular sequencing of the genes can be used to confirm the diagnosis.

The major therapeutic intervention in familial chylomicronemia syndrome is dietary fat restriction (to as little as 15 g/d) with fat-soluble vitamin supplementation. Consultation with a registered dietician familiar with this disorder is essential. Caloric supplementation with medium-chain TGs, which are absorbed directly into the portal circulation, can be useful, but there is uncertainty about their hepatic safety with prolonged use. If dietary fat restriction alone is not successful in resolving the chylomicronemia, fish oils have been effective in some patients. In patients with apoC-II deficiency, apoC-II can be provided by infusing

fresh-frozen plasma to resolve the chylomicronemia in the acute setting. Management of patients with familial chylomicronemia syndrome is particularly challenging during pregnancy when VLDL production is increased. A gene therapy approach, called alipogene tiparvovec, is approved for LPL deficiency in Europe; it involves multiple intramuscular injections of an adeno-associated viral vector encoding a gain-of-function LPL variant, leading to skeletal myocyte expression of LPL.

ApoA-V deficiency

Another apolipoprotein, ApoA-V, facilitates the association of VLDL and chylomicrons with LPL and promotes their hydrolysis. Individuals harboring loss-of-function mutations in both APOA5 alleles develop hyperchylomicronemia. Heterozygosity for variants in APOA5 that reduce its function contributes to the polygenic basis of hypertriglyceridemia.

GPIHBP1 deficiency

Homozygosity for mutations that interfere with GPIHBP1 synthesis or folding cause severe hypertriglyceridemia by compromising the transport of LPL to the vascular endothelium. The frequency of chylomicronemia due to mutations in GPIHBP1 has not been established but appears to be very rare.

Familial hypertriglyceridemia (FHTG)

FHTG is characterized by elevated fasting TGs without a clear secondary cause, average to below average LDL-C levels, low HDL-C levels, and a family history of hypertriglyceridemia. Plasma LDL-C levels are often reduced due to defective conversion of TG-rich particles to LDL. In contrast to FCHL, apoB levels are not elevated. The identification of other first-degree relatives with hypertriglyceridemia is useful in making the diagnosis. Unlike in FCHL, this condition is not generally associated with a significantly increased risk of CHD. However, if the hypertriglyceridemia is exacerbated by environmental factors, medical conditions, or drugs, the TGs can rise to a level at which acute pancreatitis is a risk. Indeed, management of patients with this condition is mostly geared toward reduction of TGs to prevent pancreatitis.

Individuals with this phenotype generally have reduced lipolysis of TRLs, although overproduction of VLDL by the liver can also contribute. No single gene has been identified in which mutations cause this disorder, whereas combinations of gene variants have been shown to cause this phenotype. A more appropriate term for this condition might be polygenic hypertriglyceridemia.

It is important to consider and rule out secondary causes of the hypertriglyceridemia as discussed above. Increased intake of simple carbohydrates, obesity, insulin resistance, alcohol use, estrogen treatment, and certain medications can exacerbate this phenotype. Patients who are at high risk for CHD due to other risk factors

should be treated with statin therapy. In patients who are otherwise not at high risk for CHD, lipid-lowering drug therapy can frequently be avoided with appropriate dietary and lifestyle changes. Patients with plasma TG levels >500 mg/dL after a trial of diet and exercise should be considered for drug therapy with a fibrate or fish oil to reduce TGs in order to prevent pancreatitis.

DYSLIPIDEMIA CAUSED BY IMPAIRED HEPATIC UPTAKE OF APOB-CONTAINING LIPOPROTEINS

Impaired uptake of LDL and remnant lipoproteins by the liver is another common cause of dyslipidemia. As discussed above, the LDL receptor is the major receptor responsible for uptake of LDL and remnant particles by the liver. Downregulation of LDL receptor activity or genetic variation that reduces the activity of the LDL receptor pathway leads to elevations in LDL-C. One major factor that reduces LDL receptor activity is a diet high in saturated and trans fats. Other medical conditions that reduce LDL receptor activity include hypothyroidism and estrogen deficiency. In addition, genetic variation in a number of genes influences LDL clearance, and mutations in some of these genes cause several discrete Mendelian disorders of elevated LDL-C (Table 37-3).

Secondary causes of impaired hepatic uptake of lipoproteins

Hypo-thyroidism

Hypothyroidism is associated with elevated plasma LDL-C levels due primarily to a reduction in hepatic LDL receptor function and delayed clearance of LDL. Thyroid hormone increases hepatic expression of the LDL receptor. Hypothyroid patients also frequently have increased levels of circulating IDL, and some patients with hypothyroidism also have mild hypertriglyceridemia. Because hypothyroidism is often subtle and therefore easily overlooked, all patients presenting with elevated plasma levels of LDL-C, especially if there has been an unexplained increase in LDL-C, should be screened for hypothyroidism. Thyroid replacement therapy usually ameliorates the hypercholesterolemia; if not, the patient probably has a primary lipoprotein disorder and may require lipid-lowering drug therapy with a statin.

Chronic kidney disease

Chronic kidney disease (CKD) is often associated with mild hypertriglyceridemia (<300 mg/dL) due to the accumulation of VLDLs and remnant lipoproteins in the circulation. TG lipolysis and remnant clearance are both reduced in patients with renal failure. Because the risk of ASCVD is increased in end-stage renal disease,

subjects with hyperlipidemia, they should usually be aggressively treated with lipid-lowering agents, even though there is inadequate data at present to indicate that this population benefits from LDL-lowering therapy.

Patients with solid organ transplants often have increased lipid levels due to the effect of the drugs required for immunosuppression. These patients can present a difficult clinical management problem, since statins should be used cautiously in these patients due to untoward muscle-related side effects.

Primary (genetic) causes of impaired hepatic uptake of lipoproteins

Genetic variation contributes substantially to elevated LDL-C levels in the general population. It has been estimated that at least 50% of variation in LDL-C is genetically determined. Many patients with elevated LDL-C have polygenic hypercholesterolemia characterized by hypercholesterolemia in the absence of secondary causes of hypercholesterolemia (other than dietary factors) or a primary Mendelian disorder. In patients who are genetically predisposed to higher LDL-C levels, diet plays a key role; indeed increased saturated and trans fats in the diet shifts the entire distribution of LDL levels in the population to the right. Inheritance of several variants that together elevate LDL-C, coupled with diet, is generally the cause of this condition; <10% of first-degree relatives themselves have hypercholesterolemia. However, single-gene (Mendelian) causes of elevated LDL-C are relatively common and should be considered in the differential diagnosis of elevated LDL-C.

Familial hypercholesterolemia (FH)

FH, also known as autosomal dominant hypercholesterolemia (ADH) type 1, is an autosomal co-dominant disorder characterized by elevated plasma levels of LDL-C in the absence of hypertriglyceridemia. FH is caused by loss-of-function mutations in the gene encoding the LDL receptor. The reduction in LDL receptor activity in the liver results in a reduced rate of clearance of LDL from the circulation. The plasma level of LDL increases to a level such that the rate of LDL production equals the rate of LDL clearance by residual LDL receptor as well as non-LDL receptor mechanisms. More than 1600 different mutations have been reported in association with FH. The elevated levels of LDL-C in FH are primarily due to delayed removal of LDL from the blood; in addition, because the removal of IDL is also delayed, the production of LDL from IDL is also increased. Individuals with two mutated LDL receptor alleles (FH homozygotes, or compound heterozygotes) have much higher LDL-C levels than those with one mutant allele (FH heterozygotes).

Heterozygous FH is caused by the inheritance of one mutant LDL receptor allele. The population frequency of heterozygous FH due to LDL receptor mutations was originally estimated to be 1 in 500 individuals, but recent data suggest it may be as high as approximately 1 in 250 individuals, making it one of the most common single-gene disorders in humans. FH has a higher prevalence in certain founder populations, such as South African Afrikaners, Christian Lebanese, and French Canadians. Heterozygous FH is characterized by elevated plasma levels of LDL-C (usually 200–400 mg/dL) and normal levels of TGs. Patients with heterozygous FH have hypercholesterolemia from birth, and disease recognition is usually based on detection of hypercholesterolemia on routine screening, the appearance of tendon xanthomas, or the development of symptomatic cardiovascular disease. Inheritance is dominant, meaning that the condition was inherited from one parent and ~50% of the patient's siblings can be expected to have hypercholesterolemia. The family history is frequently positive for premature CHD on the side of the family from which the mutation was inherited. Physical findings in many, but not all, patients with heterozygous FH include corneal arcus and tendon xanthomas particularly involving the dorsum of the hands and the Achilles tendons. Untreated heterozygous FH is associated with a markedly increased risk of cardiovascular disease. Untreated men with heterozygous FH have an ~50% chance of having a myocardial infarction before age 60 years, and women with heterozygous FH are at substantially increased risk as well. The age of onset of cardiovascular disease is highly variable and depends on the specific molecular defect, the level of LDL-C, and coexisting cardiovascular risk factors. FH heterozygotes with elevated plasma levels of Lp(a) (see below) appear to be at greater risk for cardiovascular disease.

No definitive diagnostic test for heterozygous FH is available, except in certain founder populations where selected mutations predominate. Most LDL receptor mutations are private and require sequencing of the LDL receptor gene for identification. Sequencing for clinical diagnosis is available but not standard of care and is rarely performed in the United States, because the clinical utility of identifying the specific mutation has not been demonstrated. A family history of hypercholesterolemia and/or premature coronary disease is supportive of the diagnosis. Secondary causes of significant hypercholesterolemia such as hypothyroidism, nephrotic syndrome, and obstructive liver disease should be excluded.

Heterozygous FH patients should be aggressively treated to lower plasma levels of LDL-C, starting in childhood. Initiation of a diet low in saturated and trans fats is recommended, but heterozygous FH patients

virtually always require lipid-lowering drug therapy for effective control of their LDL-C levels. Statins are effective in heterozygous FH and are clearly the drug class of choice, and usually a more potent member of the class. However, some heterozygous FH patients cannot achieve adequate control of their LDL-C levels even with high-dose statin therapy and require additional drugs; a cholesterol absorption inhibitor and/or a bile acid sequestrant are the next-line classes of drugs. Currently, heterozygous FH patients whose LDL-C levels remain markedly elevated (>200 mg/dL with cardiovascular disease [CVD] or >300 mg/dL without CVD) on maximally tolerated drug therapy are candidates for LDL apheresis, a physical method of purging the blood of LDL in which the LDL particles are selectively removed from the circulation; LDL apheresis is usually performed every 2 weeks. A new class of drugs known as PCSK9 inhibitors is under clinical development and has the potential to effectively control LDL-C levels in the vast majority of patients with heterozygous FH who are inadequately controlled on a statin alone or who are statin intolerant.

Homozygous FH is caused by mutations in both alleles of the LDL receptor and therefore much rarer than heterozygous FH. Patients with homozygous FH have been classified into those patients with virtually no detectable LDL receptor activity (receptor negative) and those patients with markedly reduced but detectable LDL receptor activity (receptor defective). LDL-C levels in patients with homozygous FH range from about 400 to >1000 mg/dL, with receptor-defective patients at the lower end and receptor-negative patients at the higher end of the range. TGs are usually normal. Many patients with homozygous FH, particularly receptor-negative patients, present in childhood with cutaneous xanthomas on the hands, wrists, elbows, knees, heels, or buttocks. The devastating consequence of homozygous FH is accelerated ASCVD, which often presents in childhood or early adulthood. Atherosclerosis often develops first in the aortic root, where it can cause aortic valvular or supraaortic stenosis, and typically extends into the coronary ostia, which become stenotic. Symptoms can be atypical, and sudden death is not uncommon. Untreated, receptor-negative patients with homozygous FH rarely survive beyond the second decade; patients with receptor-defective LDL receptor defects have a better prognosis but almost invariably develop clinically apparent atherosclerotic vascular disease by age 30, and often much sooner. Carotid and femoral disease develops later in life and is usually not clinically significant.

Homozygous FH should be suspected in a child or young adult with LDL >400 mg/dL without secondary cause. Cutaneous xanthomas, evidence of CVD, and hypercholesterolemia in both parents all are supportive

of the diagnosis. Although the specific mutations in the LDL receptor can usually be identified by DNA sequencing, this is not generally performed, and the diagnosis is usually made on clinical grounds.

Patients with homozygous FH must be treated aggressively to delay the onset and progression of CVD. Receptor defective patients sometimes respond to statins and other LDL-lowering drug classes such as a cholesterol absorption inhibitor or a bile acid sequestrant, which upregulate the LDL receptor activity. Two drugs that reduce the hepatic production of VLDL and thus LDL, a small-molecule inhibitor of the microsomal TG transfer protein (MTP) and an antisense oligonucleotide to apoB, are approved in the United States for the treatment of adults with homozygous FH and can be considered. PCSK9 inhibitors, which work through increasing LDL receptor availability, appear to have some benefit in receptor-defective patients and are under clinical development. LDL apheresis is used to lower plasma LDL levels in these patients and can promote regression of xanthomas as well as slow the progression of atherosclerosis. Because the liver is quantitatively the most important tissue for removing circulating LDLs via the LDL receptor, liver transplantation is effective in decreasing plasma LDL-C levels in this disorder but is infrequently used because of the associated problems with immunosuppression.

Familial defective apoB-100 (FDB)

FDB, also known as autosomal dominant hypercholesterolemia (ADH) type 2, is a dominantly inherited disorder that clinically resembles heterozygous FH with elevated LDL-C levels and normal TGs. FDB is caused by mutations in the gene encoding apoB-100, specifically in LDL receptor-binding domain of apoB-100. Several different mutations have been identified, but a single mutation predominates: substitution of glutamine for arginine at position 3500. The mutation results in a reduction in the affinity of LDL binding to the LDL receptor, so LDL is removed from the circulation at a reduced rate. FDB is less common than FH but is more prevalent in individuals of central European descent; the Lancaster County (United States) Amish are a founder population in which the prevalence of FDB is as high as 1 in 10 individuals. FDB is characterized by elevated plasma LDL-C levels with normal TGs; tendon xanthomas can be seen, although not as frequently as in FH, and there is an associated increase in risk of CHD. Patients with FDB cannot be clinically distinguished from patients with heterozygous FH, although patients with FDB tend to have somewhat lower plasma levels of LDL-C than FH heterozygotes, presumably due to the fact that IDL clearance is not impaired in this disorder. Homozygotes for FDB mutations have higher LDL-C levels than FDB heterozygotes but are not as

severely affected as homozygous FH patients. The apoB-100 gene mutations can be detected directly through sequencing of the receptor-binding region of the apoB gene or genotyping for the most common mutation, but genetic diagnosis is not generally performed because there is no direct implication for clinical management. As with FH, patients are treated with statins first and, if necessary, with additional classes of LDL-lowering drugs.

Autosomal dominant hypercholesterolemia due to mutations in PCSK9 (ADH-PCSK9 or ADH3)

ADH-PCSK9, also known as autosomal dominant hypercholesterolemia (ADH) type 3, is a very rare autosomal dominant disorder caused by gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a secreted protein that binds to the LDL receptor, targeting it for degradation. Normally, after LDL binds to the LDL receptor, it is internalized along with the receptor, and in the low pH of the endosome, the LDL receptor dissociates from the LDL and recycles to the cell surface. When PCSK9 binds the receptor, the complex is internalized and the receptor is directed to the lysosome, rather than to the cell surface. The missense mutations in PCSK9 that cause hypercholesterolemia enhance the activity of PCSK9. As a consequence, the number of hepatic LDL receptors is reduced. Patients with ADH-PCSK9 are similar clinically to patients with FH. They may be particularly responsive to PCSK9 inhibitors in clinical development. Loss-of-function mutations in PCSK9 cause low LDL-C levels (see below).

Autosomal recessive hypercholesterolemia (ARH)

ARH is a very rare disorder that is mostly seen in individuals of Sardinian descent. The disease is caused by mutations in a protein, ARH (also called LDLR adaptor protein, LDLRAP), which is required for LDL receptor-mediated endocytosis in the liver. ARH binds to the cytoplasmic domain of the LDL receptor and links the receptor to the endocytic machinery. In the absence of LDLRAP, LDL binds to the extracellular domain of the LDL receptor, but the lipoprotein-receptor complex fails to be internalized. ARH, like homozygous FH, is characterized by hypercholesterolemia, tendon xanthomas, and premature coronary artery disease (CAD). The levels of plasma LDL-C tend to be intermediate between the levels present in FH homozygotes and FH heterozygotes, and CAD is not usually symptomatic until the third decade. LDL receptor function in cultured fibroblasts is normal or only modestly reduced in ARH, whereas LDL receptor function in lymphocytes and the liver is negligible. Unlike FH homozygotes, the hyperlipidemia responds to treatment with statins, but these

patients usually require additional therapy to lower plasma LDL-C to acceptable levels.

Sitosterolemia

Sitosterolemia is a rare autosomal recessive disease that can result in severe hypercholesterolemia, tendon xanthomas, and premature ASCVD. Sitosterolemia is caused by loss-of-function mutations in either of two members of the ATP-binding cassette (ABC) half transporter family, ABCG5 and ABCG8. These genes are expressed in enterocytes and hepatocytes. The proteins heterodimerize to form a functional complex that transports plant sterols such as sitosterol and campesterol, and animal sterols, predominantly cholesterol, across the biliary membrane of hepatocytes into the bile and across the intestinal luminal surface of enterocytes into the gut lumen. In normal individuals, <5% of dietary plant sterols are absorbed by the proximal small intestine. The small amounts of plant sterols that enter the circulation are preferentially excreted into the bile. Thus, levels of plant sterols are kept very low in tissues. In sitosterolemia, the intestinal absorption of sterols is increased and biliary and fecal excretion of the sterols is reduced, resulting in increased plasma and tissue levels of both plant sterols and cholesterol. The increase in hepatic sterol levels results in transcriptional suppression of the expression of the LDL receptor, resulting in reduced uptake of LDL and substantially increased LDL-C levels. In addition to the usual clinical picture of hypercholesterolemia (i.e., tendon xanthomas and premature ASCVD), these patients also have anisocytosis and poikilocytosis of erythrocytes and megathrombocytes due to the incorporation of plant sterols into cell membranes. Episodes of hemolysis and splenomegaly are a distinctive clinical feature of this disease compared to other genetic forms of hypercholesterolemia and can be a clue to the diagnosis.

Sitosterolemia should be suspected in a patient with severe hypercholesterolemia without a family history of such or who responds dramatically to dietary therapy and/or ezetimibe but not statins. Sitosterolemia can be diagnosed by a laboratory finding of a substantial increase in the plasma level of sitosterol and/or other plant sterols. It is important to make the diagnosis, because bile acid sequestrants and cholesterol-absorption inhibitors are the most effective agents to reduce LDL-C and plasma plant sterol levels in these patients.

Cholesteryl ester storage disease (CESD)

CESD, also known as lysosomal acid lipase deficiency, is an autosomal recessive disorder characterized by elevated LDL-C, usually in association with low HDL-C, together with progressive fatty liver ultimately leading to hepatic fibrosis. Plasma TG levels can also be mild to moderately increased in this disorder. The most severe form of this disorder, Wolman's disease, presents in

infancy and is rapidly fatal. Both Wolman's disease and CESD are caused by loss-of-function variants in both alleles of the gene encoding lysosomal acid lipase (LAL; gene name LIPA). LAL is responsible for hydrolyzing neutral lipids, particularly TGs and cholesteryl esters, after delivery to the lysosome by cell-surface receptors such as the LDL receptor. It is particularly important in the liver, which clears large amounts of lipoproteins from the circulation. Genetic deficiency of LAL results in accumulation of neutral lipid in the hepatocytes, leading to hepatosplenomegaly, microvesicular steatosis, and ultimately fibrosis and end-stage liver disease. The etiology of the elevated LDL-C levels is uncertain; one study suggested that VLDL production is increased, but impaired LDL receptor-mediated clearance of LDL is also likely.

CESD should be particularly suspected in nonobese patients with elevated LDL-C, low HDL-C, and evidence of fatty liver in the absence of overt insulin resistance. The diagnosis can be made with a dried blood spot assay of LAL activity and confirmed by DNA genotyping for the most common mutation, followed if necessary by sequencing of the gene to find the second mutation. Liver biopsy is required to assess the degree of inflammation and fibrosis. It is important to make the diagnosis because it has implications for liver monitoring and potentially for therapeutic approaches under development.

Familial dysbetalipoproteinemia (FDBL)

FDBL (also known as type III hyperlipoproteinemia) is usually a recessive disorder characterized by a mixed hyperlipidemia (elevated cholesterol and TGs) due to the accumulation of remnant lipoprotein particles (chylomicron remnants and VLDL remnants, or IDL). ApoE is present in multiple copies on chylomicron remnants and IDL, and mediates their removal via hepatic lipoprotein receptors (Fig. 37-2). FDBL is due to genetic variants of apoE, most commonly apoE2, that result in an apoE protein with reduced ability to bind lipoprotein receptors. The APOE gene is polymorphic in sequence, resulting in the expression of three common isoforms: apoE3, which is the most common; and apoE2 and apoE4, which both differ from apoE3 by a single amino acid. Although associated with slightly higher LDL-C levels and increased CHD risk, the apoE4 allele is not associated with FDBL. Individuals who carry one or two apoE4 alleles have an increased risk of Alzheimer's disease. ApoE2 has a lower affinity for the LDL receptor; therefore, chylomicron remnants and IDL containing apoE2 are removed from plasma at a slower rate. Individuals who are homozygous for the E2 allele (the E2/E2 genotype) comprise the most common subset of patients with FDBL.

Approximately 0.5% of the general population are apoE2/E2 homozygotes, but only a small minority of

these individuals actually develop hyperlipidemia characteristic of FDBL. In most cases, an additional, sometimes identifiable, factor precipitates the development of hyperlipoproteinemia. The most common precipitating factors are a high-fat diet, diabetes mellitus, obesity, hypothyroidism, renal disease, HIV infection, estrogen deficiency, alcohol use, or certain drugs. The disease seldom presents in women before menopause. Other mutations in apoE can cause a dominant form of FDBL where the hyperlipidemia is fully manifest in the heterozygous state, but these mutations are very rare.

Patients with FDBL usually present in adulthood with hyperlipidemia, xanthomas, or premature coronary or peripheral vascular disease. In FDBL, in contrast to other disorders of elevated TGs, the plasma levels of cholesterol and TG are often elevated to a similar degree, and the level of HDL-C is usually normal or reduced. Two distinctive types of xanthomas, tuberous and palmar, are seen in FDBL patients. Tuberous xanthomas begin as clusters of small papules on the elbows, knees, or buttocks and can grow to the size of small grapes. Palmar xanthomas (alternatively called xanthomata striata palmaris) are orange-yellow discolorations of the creases in the palms and wrists. Both of these xanthoma types are virtually pathognomonic for FDBL. Subjects with FDBL have premature ASCVD and tend to have more peripheral vascular disease than is typically seen in FH.

The definitive diagnosis of FDBL can be made either by the documentation of very high levels of remnant lipoproteins or by identification of the apoE2/E2 genotype. A variety of methods are used to identify remnant lipoproteins in the plasma, including "β-quantification" by ultracentrifugation (ratio of directly measured VLDL-C to total plasma TG >0.30), lipoprotein electrophoresis (broad β band), or nuclear magnetic resonance lipoprotein profiling. The Friedewald formula for calculation of LDL-C is not valid in FDBL because the VLDL particles are depleted in TG and enriched in cholesterol. The plasma levels of LDL-C are actually low in this disorder due to defective metabolism of VLDL to LDL. DNA-based methods (apoE genotyping) can be performed to confirm homozygosity for apoE2. However, absence of the apoE2/E2 genotype does not strictly rule out the diagnosis of FDBL, because other mutations in apoE can (rarely) cause this condition.

Because FDBL is associated with increased risk of premature ASCVD, it should be treated aggressively. Other metabolic conditions that can worsen the hyperlipidemia (see above) should be managed. Patients with FDBL are typically diet-responsive and can respond favorably to weight reduction and to low-cholesterol, low-fat diets. Alcohol intake should be curtailed. Pharmacologic therapy is often required, and statins are the first line in management. In the event of statin

TABLE 37-4

SECONDARY CAUSES OF DYSLIPIDEMIA							
LDL		HDL		VLDL	IDL	CHYLOMICRONS	LP(A)
ELEVATED	REDUCED	ELEVATED	REDUCED	ELEVATED	ELEVATED	ELEVATED	ELEVATED
Hypothyroidism	Severe liver disease	Alcohol	Smoking	Obesity	Multiple myeloma	Autoimmune disease	Chronic kidney disease Nephrotic syndrome
Nephrotic syndrome Cholestasis	Malabsorption Malnutrition Gaucher's disease	Exercise Exposure to chlorinated hydrocarbons	DM type 2 Obesity Malnutrition	DM type 2 Glycogen storage disease	Monoclonal gammopathy	DM type 2	Inflammation Menopause
Acute intermittent porphyria	Chronic infectious disease	Drugs: estrogen	Gaucher's disease	Nephrotic syndrome Hepatitis Alcohol	Autoimmune disease		Orchidectomy
Anorexia nervosa Hepatoma Drugs: thiazides, cyclosporin, carbamazepine	Hyperthyroidism Drugs: niacin toxicity		Cholesteryl ester storage disease Drugs: anabolic steroids, beta blockers	Renal failure Sepsis Stress Cushing's syndrome Pregnancy Acromegaly Lipodystrophy Drugs: estrogen, beta blockers, glucocorticoids, bile acid binding resins, retinoic acid	Hypothyroidism		Hypothyroidism Acromegaly Drugs: growth hormone, isotretinoin

Abbreviations: DM, diabetes mellitus; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein A; VLDL, very-low-density lipoprotein.

intolerance or insufficient control of hyperlipidemia, cholesterol absorption inhibitors, fibrates, and niacin are also effective in the treatment of FDBL.

Hepatic lipase deficiency

Hepatic lipase (HL; gene name LIPC) is a member of the same gene family as LPL and hydrolyzes TGs and phospholipids in remnant lipoproteins and HDL. Hydrolysis of lipids in remnant particles by HL contributes to their hepatic uptake via an apoE-mediated process. HL deficiency is a very rare autosomal recessive disorder characterized by elevated plasma levels of cholesterol and TGs (mixed hyperlipidemia) due to the accumulation of lipoprotein remnants, accompanied by elevated plasma level of HDL-C. The diagnosis is confirmed by measuring HL activity in postheparin plasma and/or confirmation of loss-of-function mutations in both alleles of HL/LIPC. Due to the small number of patients with HL deficiency, the association of this genetic defect with ASCVD is not entirely clear, although anecdotally patients with

HL deficiency who have premature CVD have been described. As with FDBL, statin therapy is recommended to reduce remnant lipoproteins and cardiovascular risk.

Additional secondary causes of dyslipidemia

Many of the secondary causes of dyslipidemia (Table 37-4) have been described above. Additional considerations are discussed here.

Liver disorders

Because the liver is the principal site of formation and clearance of lipoproteins, liver disorders can affect plasma lipid levels in a variety of ways. Hepatitis due to infection, drugs, or alcohol is often associated with increased VLDL synthesis and mild to moderate hypertriglyceridemia. Severe hepatitis and liver failure are associated with dramatic reductions in plasma cholesterol and TGs due to reduced lipoprotein biosynthetic capacity.

Cholestasis is associated with hypercholesterolemia, which can be very severe. A major pathway by which cholesterol is excreted from the body is via secretion into bile, either directly or after conversion to bile acids, and cholestasis blocks this critical excretory pathway. In cholestasis, free cholesterol, coupled with phospholipids, is secreted into the plasma as a constituent of a lamellar particle called LP-X. The particles can deposit in skinfolds, producing lesions resembling those seen in patients with FDBL (xanthomata strata palmaris). Planar and eruptive xanthomas can also be seen in patients with cholestasis.

Drugs

Many drugs have an impact on lipid metabolism and can result in significant alterations in the lipoprotein profile (Table 37-4). Estrogen administration is associated with increased VLDL and HDL synthesis, resulting in elevated plasma levels of both TGs and HDL-C. This lipoprotein pattern is distinctive because the levels of plasma TG and HDL-C are typically inversely related. Plasma TG levels should be monitored when birth control pills or postmenopausal estrogen therapy is initiated to ensure that the increase in VLDL production does not lead to severe hypertriglyceridemia. Use of low-dose preparations of estrogen or the estrogen patch can minimize the effect of exogenous estrogen on lipids.

INHERITED CAUSES OF LOW LEVELS OF ApoB-CONTAINING LIPOPROTEINS

Plasma concentrations of LDL-C <60 mg/dL are unusual. Although in some cases LDL-C levels in this range may be reflective of malnutrition or serious chronic illness, LDL-C <60 mg/dL in an otherwise healthy individual suggests an inherited condition. The major inherited causes of low LDL-C are reviewed here.

Abetalipoproteinemia

The synthesis and secretion of apoB-containing lipoproteins in the enterocytes of the proximal small bowel and in the hepatocytes of the liver involve a complex series of events that coordinate the coupling of various lipids with apoB-48 and apoB-100, respectively. Abetalipoproteinemia is a rare autosomal recessive disease caused by loss-of-function mutations in the gene encoding microsomal TG transfer protein (MTP; gene name MTTP), a protein that transfers lipids to nascent chylomicrons and VLDLs in the intestine and liver, respectively. Plasma levels of cholesterol and TG are extremely low in this disorder, and chylomicrons, VLDLs, LDLs, and apoB are undetectable in plasma. The parents of patients with abetalipoproteinemia (obligate heterozygotes) have normal plasma lipid and apoB levels. Abetalipoproteinemia usually presents in early childhood

with diarrhea and failure to thrive due to fat malabsorption. The initial neurologic manifestations are loss of deep tendon reflexes, followed by decreased distal lower extremity vibratory and proprioceptive sense, dysmetria, ataxia, and the development of a spastic gait, often by the third or fourth decade. Patients with abetalipoproteinemia also develop a progressive pigmented retinopathy presenting with decreased night and color vision, followed by reductions in daytime visual acuity and ultimately progressing to near-blindness. The presence of spinocerebellar degeneration and pigmented retinopathy in this disease has resulted in some patients with abetalipoproteinemia being misdiagnosed as having Friedreich's ataxia.

Most of the clinical manifestations of abetalipoproteinemia result from defects in the absorption and transport of fat-soluble vitamins. Vitamin E and retinyl esters are normally transported from enterocytes to the liver by chylomicrons, and vitamin E is dependent on VLDL for transport out of the liver and into the circulation. As a consequence of the inability of these patients to secrete apoB-containing particles, patients with abetalipoproteinemia are markedly deficient in vitamin E and are also mildly to moderately deficient in vitamins A and K. Patients with abetalipoproteinemia should be referred to specialized centers for confirmation of the diagnosis and appropriate therapy. Treatment consists of a low-fat, high-caloric, vitamin-enriched diet accompanied by large supplemental doses of vitamin E. It is imperative that treatment be initiated as soon as possible to prevent development of neurologic sequelae, which can progress even with appropriate therapy. New therapies for this serious disease are needed.

Familial hypobetalipoproteinemia (FHBL)

FHBL generally refers to a condition of low total cholesterol, LDL-C, and apoB due to mutations in apoB. Most of the mutations causing FHBL result in a truncated apoB protein, resulting in impaired assembly and secretion of chylomicrons from enterocytes and VLDL from the liver. Mutations that result in VLDL particles containing a truncated apoB protein are cleared from the circulation at an accelerated rate, which also contributes to patients with this disorder having low levels of LDL-C and apoB. Individuals heterozygous for these mutations usually have LDL-C levels <60 – 80 mg/dL and also tend to have lower levels of plasma TG. Many FHBL patients have elevated levels of hepatic fat (due to reduced VLDL export) and sometimes have increased levels of liver transaminases, although it appears that these patients infrequently develop associated inflammation and fibrosis.

Mutations in both apoB alleles cause homozygous FHBL, an extremely rare disorder resembling abetalipoproteinemia with nearly undetectable LDL-C and

apoB. The neurologic defects in this form of hypobetalipoproteinemia tend to be less severe than is typically seen in abetalipoproteinemia. Homozygous hypobetalipoproteinemia can be distinguished from abetalipoproteinemia by examining the inheritance pattern of the plasma LDL-C level. The levels of LDL-C and apoB are normal in the parents of patients with abetalipoproteinemia and low in those of patients with homozygous hypobetalipoproteinemia.

PCSK9 deficiency

Another inherited cause of low LDL-C results from loss-of-function mutations in PCSK9. PCSK9 is a secreted protein that binds to the extracellular domain of the LDL receptor in the liver and promotes the degradation of the receptor. Heterozygosity for nonsense mutations in PCSK9 that interfere with the synthesis of the protein are associated with increased hepatic LDL receptor activity and reduced plasma levels of LDL-C. Such mutations are particularly frequent in individuals of African descent. Individuals who are heterozygous for a loss-of-function mutation in PCSK9 have an ~30–40% reduction in plasma levels of LDL-C and have a substantial protection from CHD relative to those without a PCSK9 mutation, presumably due to having lower plasma cholesterol levels since birth. This observation led to the development of PCSK9 inhibitors as a new strategy for reducing LDL-C levels and cardiovascular risk. Homozygotes for these nonsense mutations have been reported and have extremely low LDL-C levels (<20 mg/dL) but appear otherwise healthy. A sequence variation of somewhat higher frequency (R46L) is found predominantly in individuals of European descent. This mutation impairs, but does not completely destroy, PCSK9 function. As a consequence, the plasma levels of LDL-C in individuals carrying this mutation are more modestly reduced (~15–20%); individuals with these mutations have a 45% reduction in ASCVD risk.

DISORDERS OF REDUCED HDL CHOLESTEROL

Low levels of HDL-C are very commonly encountered in clinical practice. Low HDL-C is an important independent predictor of increased cardiovascular risk and has been used regularly in standardized risk calculators, including the most recent one from the American Heart Association (AHA)/American College of Cardiology (ACC). However, it remains very uncertain whether low HDL-C is directly causal for the development of ASCVD. HDL metabolism is strongly influenced by TRLs, insulin resistance, and inflammation, among other environmental and medical factors. Thus

the HDL-C measurement integrates a number of cardiovascular risk factors, potentially explaining its strong inverse association with ASCVD.

The majority of patients with low HDL-C have some combination of genetic predisposition and secondary factors. Variants in dozens of genes have been shown to influence HDL-C levels. Even more important quantitatively, obesity and insulin resistance have strong suppressive effects on HDL-C, and low HDL-C in these conditions is widely observed. Furthermore, the vast majority of patients with elevated TGs have reduced levels of HDL-C. Most patients with low HDL-C who have been studied in detail have accelerated catabolism of HDL and its associated apoA-I as the physiologic basis for the low HDL-C. Importantly, although HDL-C remains an important biomarker for assessing cardiovascular risk, it is not currently a direct target of intervention for raising the level in order to reduce cardiovascular risk. Certain therapeutic approaches in clinical development, such as inhibitors of CETP (see below), have the potential to change this paradigm.

INHERITED CAUSES OF VERY LOW LEVELS OF HDL-C

Mutations in genes encoding proteins that play critical roles in HDL synthesis and catabolism can result in reductions in plasma levels of HDL-C. Unlike the genetic forms of hypercholesterolemia, which are invariably associated with premature coronary atherosclerosis, genetic forms of hypoalphalipoproteinemia (low HDL-C) are often not associated with clearly increased risk of ASCVD.

Gene deletions in the APOA5-A1-C3-A4 locus and coding mutations in APOA1

Complete genetic deficiency of apoA-I due to a complete deletion of the APOA1 gene results in the virtual absence of circulating HDL and appears to increase the risk of premature ASCVD. The genes encoding APOA5, APOA1, APOC3, and APOA4 are clustered together on chromosome 11. Some patients with no apoA-I have genomic deletions that include other genes in the cluster. ApoA-I is required for LCAT activity. In the absence of LCAT, free cholesterol levels increase in both plasma (not HDL) and in tissues. The free cholesterol can form deposits in the cornea and in the skin, resulting in corneal opacities and planar xanthomas. Premature CHD is associated with apoA-I deficiency.

Missense and nonsense mutations in the apoA-I gene are present in some patients with low plasma levels of HDL-C (usually 15–30 mg/dL), but are a rare cause of low plasma HDL-C levels. Most individuals with low plasma HDL-C levels due to missense mutations in apoA-I do not appear to have premature CHD. Patients

who are heterozygous for an Arg173Cys substitution in apoA-I (so-called apoA-I_{Milano}) have very low plasma levels of HDL-C due to impaired LCAT activation and accelerated clearance of the HDL particles containing the abnormal apoA-I. Despite having very low plasma levels of HDL-C, these individuals do not have an increased risk of premature CHD.

A few selected missense mutations in apoA-I and apoA-II promote the formation of amyloid fibrils, which can cause systemic amyloidosis.

Tangier disease (ABCA1 deficiency)

Tangier disease is a rare autosomal co-dominant form of extremely low plasma HDL-C levels that is caused by mutations in the gene encoding ABCA1, a cellular transporter that facilitates efflux of unesterified cholesterol and phospholipids from cells to apoA-I (Fig. 37-3). ABCA1 in the liver and intestine rapidly lipidates the apoA-I secreted from the basolateral membranes of these tissues. In the absence of ABCA1, the nascent, poorly lipidated apoA-I is immediately cleared from the circulation. Thus, patients with Tangier disease have extremely low circulating plasma levels of HDL-C (<5 mg/dL) and apoA-I (<5 mg/dL). Cholesterol accumulates in the reticuloendothelial system of these patients, resulting in hepatosplenomegaly and pathognomonic enlarged, grayish yellow or orange tonsils. An intermittent peripheral neuropathy (mononeuritis multiplex) or a sphingomyelia-like neurologic disorder can also be seen in this disorder. Tangier disease is probably associated with some increased risk of premature atherosclerotic disease, although the association is not as robust as might be anticipated, given the very low levels of HDL-C and apoA-I in these patients. Patients with Tangier disease also have low plasma levels of LDL-C, which may attenuate the atherosclerotic risk. Obligate heterozygotes for ABCA1 mutations have moderately reduced plasma HDL-C levels (15–30 mg/dL), and their risk of premature CHD remains uncertain.

Familial LCAT deficiency

This rare autosomal recessive disorder is caused by mutations in LCAT, an enzyme synthesized in the liver and secreted into the plasma, where it circulates associated with lipoproteins (Fig. 37-3). As reviewed above, the enzyme is activated by apoA-I and mediates the esterification of cholesterol to form cholesteryl esters. Consequently, in familial LCAT deficiency, the proportion of free cholesterol in circulating lipoproteins is greatly increased (from ~25% to >70% of total plasma cholesterol). Deficiency in this enzyme interferes with the maturation of HDL particles and results in rapid catabolism of circulating apoA-I.

Two genetic forms of familial LCAT deficiency have been described in humans: complete deficiency (also called classic LCAT deficiency) and partial deficiency (also called fish-eye disease). Progressive corneal opacification due to the deposition of free cholesterol in the cornea, very low plasma levels of HDL-C (usually <10 mg/dL), and variable hypertriglyceridemia are characteristic of both disorders. In partial LCAT deficiency, there are no other known clinical sequelae. In contrast, patients with complete LCAT deficiency have hemolytic anemia and progressive renal insufficiency that eventually leads to end-stage renal disease. Remarkably, despite the extremely low plasma levels of HDL-C and apoA-I, premature ASCVD is not a consistent feature of either LCAT deficiency or fish eye disease. The diagnosis can be confirmed in a specialized laboratory by assaying plasma LCAT activity or by sequencing the LCAT gene.

Primary hypoalphalipoproteinemia

The condition of low plasma levels of HDL-C (the “alpha lipoprotein”) is referred to as hypoalphalipoproteinemia. Primary hypoalphalipoproteinemia is defined as a plasma HDL-C level below the tenth percentile in the setting of relatively normal cholesterol and TG levels, no apparent secondary causes of low plasma HDL-C, and no clinical signs of LCAT deficiency or Tangier disease. This syndrome is often referred to as isolated low HDL. A family history of low HDL-C facilitates the diagnosis of an inherited condition, which may follow an autosomal dominant pattern. The metabolic etiology of this disease appears to be primarily accelerated catabolism of HDL and its apolipoproteins. Some of these patients may have ABCA1 mutations and therefore technically have heterozygous Tangier disease. Several kindreds with primary hypoalphalipoproteinemia and an increased incidence of premature CHD have been described, although it is not clear if the low HDL-C level is the cause of the accelerated atherosclerosis in these families. Association of hypoalphalipoproteinemia with premature CHD may depend on the specific nature of the gene defect or the underlying metabolic defect that either directly or indirectly causes the low plasma HDL-C level.

INHERITED CAUSES OF VERY HIGH LEVELS OF HDL-C

CETP deficiency

Loss-of-function mutations in both alleles of the gene encoding CETP cause substantially elevated HDL-C levels (usually >150 mg/dL). As noted above, CETP transfers cholesteryl esters from HDL to apoB-containing lipoproteins (Fig. 37-3). Absence of this transfer activity

results in an increase in the cholesteryl ester content of HDL and a reduction in plasma levels of LDL-C. The large, cholesterol-rich HDL particles circulating in these patients are cleared at a reduced rate. CETP deficiency was first diagnosed in Japanese persons and is rare outside of Japan. The relationship of CETP deficiency to ASCVD remains unresolved. Heterozygotes for CETP deficiency have only modestly elevated HDL-C levels. Based on the phenotype of high HDL-C in CETP deficiency, pharmacologic inhibition of CETP is under development as a new therapeutic approach to both raise HDL-C levels and lower LDL-C levels, but whether it will reduce risk of ASCVD remains to be determined.

SCREENING, DIAGNOSIS, AND MANAGEMENT OF DISORDERS OF LIPOPROTEIN METABOLISM

SCREENING

Plasma lipid and lipoprotein levels should be measured in all adults, preferably after a 12-h overnight fast. In most clinical laboratories, the total cholesterol and TGs in the plasma are measured enzymatically, and then the cholesterol in the supernatant is measured after precipitation of apoB-containing lipoproteins to determine the HDL-C. The LDL-C is then estimated using the following equation: $\text{LDL-C} = \text{total cholesterol} - (\text{TG}/5) - \text{HDL-C}$

(The VLDL cholesterol content is estimated by dividing the plasma TG by 5, reflecting the ratio of TG to cholesterol in VLDL particles.) This formula (the Friedewald formula) is reasonably accurate if test results are obtained on fasting plasma and if the TG level does not exceed ~200 mg/dL; by convention it cannot be used if the TG level is >400 mg/dL. LDL-C can be directly measured by a number of methods. Further evaluation and treatment are based primarily on the clinical assessment of absolute cardiovascular risk using risk calculators such as the AHA/ACC risk calculator based on a large amount of observational data.

DIAGNOSIS

A critical first step in managing a lipoprotein disorder is to attempt to determine the class or classes of lipoproteins that are increased or decreased in the patient. Once the hyperlipidemia is accurately classified, efforts should be directed to rule out any possible secondary causes of the hyperlipidemia (Table 37-4). Although many patients with hyperlipidemia have a primary (i.e., genetic) cause of their lipid disorder, secondary factors frequently contribute to the hyperlipidemia. A careful social, medical, and family history should be obtained. A fasting glucose should be obtained in

the initial workup of all subjects with an elevated TG level. Nephrotic syndrome and chronic renal insufficiency should be excluded by obtaining urine protein and serum creatinine. Liver function tests should be performed to rule out hepatitis and cholestasis. Hypothyroidism should be ruled out by measuring serum thyroid-stimulating hormone.

Once secondary causes have been ruled out, attempts should be made to diagnose the primary lipid disorder because the underlying genetic defect can provide important prognostic information regarding the risk of developing CHD, the response to drug therapy, and the management of other family members. Obtaining the correct diagnosis often requires a detailed family medical history, lipid analyses in family members, and sometimes specialized testing.

Severe hypertriglyceridemia

If the fasting plasma TG level is >1000 mg/dL, the patient has chylomicronemia. If the cholesterol-to-TG ratio is >10, familial chylomicronemia syndrome must be considered, and LPL activity measured in postheparin plasma can help with making that diagnosis. Most adults with chylomicronemia also have elevated VLDL levels. These individuals usually do not have a Mendelian disorder but instead are genetically predisposed and have secondary factors (diet, obesity, glucose intolerance, alcohol ingestion, estrogen therapy) that contribute to the hyperlipidemia. Such patients are at risk of acute pancreatitis and should be treated to reduce their TG levels and thus their risk of pancreatitis.

Severe hypercholesterolemia

If the levels of LDL-C are very high (greater than a ninety-fifth percentile for age and sex), it is likely that the patient has a genetic cause of hypercholesterolemia. At present, there is no compelling reason to perform molecular studies to further refine the molecular diagnosis because the clinical management is not affected. Recessive forms of severe hypercholesterolemia are rare, but if a patient with severe hypercholesterolemia has parents with normal cholesterol levels, ARH, sitosterolemia, and CESD should be considered. Patients with more moderate hypercholesterolemia that does not segregate in families as a monogenic trait are likely to have polygenic hypercholesterolemia.

Combined hyperlipidemia

The most common errors in the diagnosis of lipid disorders involve patients with combined hyperlipidemia. Elevations in the plasma levels of both cholesterol and TGs are seen in patients with increased plasma levels of VLDL and LDL or of remnant lipoproteins. A

β -quantification to determine the VLDL cholesterol/TG ratio in plasma (see discussion of FDBL) or a direct measurement of the plasma LDL-C should be performed at least once prior to initiation of lipid-lowering therapy to determine if the hyperlipidemia is due to the accumulation of remnants or to an increase in both LDL and VLDL. Measurement of plasma apoB levels can help identify patients with FCHL who may require more aggressive treatment.

APPROACH TO THE PATIENT

Lipoprotein Disorders

The major goals in the clinical management of lipoprotein disorders are: (1) prevention of acute pancreatitis in patients with severe hypertriglyceridemia; and (2) prevention of CVD and related cardiovascular events.

MANAGEMENT OF SEVERE HYPERTRIGLYCERIDEMIA TO PREVENT PANCREATITIS Although the observational relationship between severe hypertriglyceridemia, particularly chylomicronemia, and acute pancreatitis is well-established, there has never been a clinical trial designed or powered to prove that intervention to reduce TGs reduces the risk of pancreatitis. Nevertheless, it is generally considered appropriate medical practice to intervene in patients with TGs >500 mg/dL in order to reduce the risk of pancreatitis. It remains controversial whether individuals with severe hypertriglyceridemia are at increased risk for ASCVD.

Lifestyle Modifying the lifestyle of the patient with severe hypertriglyceridemia often is associated with a significant reduction in plasma TG level. Patients who drink alcohol should be encouraged to decrease or preferably eliminate their intake. Patients with severe hypertriglyceridemia often benefit from a formal dietary consultation with a dietician intimately familiar with counseling patients on the dietary management of high TGs. Dietary fat intake should be restricted to reduce the formation of chylomicrons in the intestine. The excessive intake of simple carbohydrates should be discouraged because insulin drives TG production in the liver. Aerobic exercise and even increase in regular physical activity can have a positive effect in reducing TG levels and should be strongly encouraged. For patients who are overweight, weight loss can help to reduce TG levels. In extreme cases, bariatric surgery has been shown to not only produce effective weight loss but also substantially reduce plasma TG levels.

Pharmacologic Therapy for Severe Hypertriglyceridemia Despite the above interventions, however, many patients with severe hypertriglyceridemia require pharmacologic therapy (**Table 37-5**). Patients who persist in having fasting TG >500 mg/dL despite active lifestyle management are candidates for pharmacologic therapy. There are three classes

of drugs that are used for management of these patients: fibrates, omega-3 fatty acids (fish oils), and niacin. In addition, statins can reduce plasma TG levels and also reduce ASCVD risk.

Fibrates Fibrates are fibric acid derivatives, or fibrates, are agonists of PPAR α , a nuclear receptor involved in the regulation of lipid metabolism. Fibrates stimulate LPL activity (enhancing TG hydrolysis), reduce apoC-III synthesis (enhancing lipoprotein remnant clearance), promote β -oxidation of fatty acids, and may reduce VLDL TG production. Fibrates are a first-line therapy for severe hypertriglyceridemia (>500 mg/dL). This class of therapeutic agents sometimes lowers but more often raises the plasma level of LDL-C in individuals with severe hypertriglyceridemia. Fibrates are generally well tolerated, but are associated with an increase in the incidence of gallstones. Fibrates can cause myopathy, especially when combined with other lipid-lowering therapy (statins, niacin), and can raise creatinine. Fibrates should be used with caution in patients with CKD. Importantly, fibrates can potentiate the effect of warfarin and certain oral hypoglycemic agents, so the anticoagulation status and plasma glucose levels should be closely monitored in patients on these agents.

Omega 3 Fatty Acids (Fish Oils) Omega-3 fatty acids, or omega-3 polyunsaturated fatty acids (n-3 PUFAs), commonly known as fish oils, are present in high concentration in fish and in flaxseed. The most widely used n-3 PUFAs for the treatment of hyperlipidemias are the two active molecules in fish oil: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). n-3 PUFAs have been concentrated into tablets and in doses of 3–4 g/d are effective at lowering fasting TG levels. Fish oils are a reasonable consideration for first-line therapy in patients with severe hypertriglyceridemia (>500 mg/dL) to prevent pancreatitis. Fish oils can cause an increase in plasma LDL-C levels in some patients. In general, fish oils are well tolerated, with the major side effect being dyspepsia. They appear to be safe, at least at doses up to 3–4 g, but can be associated with a prolongation in the bleeding time.

Nicotinic acid Nicotinic acid, or niacin, is a B-complex vitamin that has been used as a lipid-modifying agent for more than five decades. Niacin suppresses lipolysis in the adipocyte through its effect on the niacin receptor GPR109A and has other effects on hepatic lipid metabolism that are poorly understood. Niacin reduces plasma TG and LDL-C levels and also raises the plasma concentration of HDL-C. Because it has a number of side effects and can be difficult to use, it is at best a third-line agent for the management of severe hypertriglyceridemia. Niacin therapy is generally started at lower doses and gradually titrated up to higher doses. The most frequent side effect of niacin is cutaneous flushing, which is mediated by activating GPR109A in the skin. Niacin can cause dyspepsia and can exacerbate esophageal reflux and peptic ulcer disease. Mild elevations in transaminases occur in up to 15% of

TABLE 3 7-5

SUMMARY OF THE MAJOR APPROVED DRUGS USED FOR THE TREATMENT OF DYSLIPIDEMIA					
DRUG	MAJOR INDICATIONS	STARTING DOSE	MAXIMAL DOSE	MECHANISM	COMMON SIDE EFFECTS
HMG-CoA reductase inhibitors (statins)	Elevated LDL-C; increased CV risk			↓ Cholesterol synthesis, ↑ Hepatic LDL receptors, ↓ VLDL production	Myalgias, arthralgias, elevated transaminases, dyspepsia
Lovastatin		20–40 mg daily	80 mg daily		
Pravastatin		40–80 mg daily	80 mg daily		
Simvastatin		20–40 mg daily	80 mg daily		
Fluvastatin		20–40 mg daily	80 mg daily		
Atorvastatin		20–40 mg daily	80 mg daily		
Rosuvastatin		5–20 mg daily	40 mg daily		
Pitavastatin		1–2 mg daily	4 mg daily		
Cholesterol absorption inhibitor	Elevated LDL-C			↓ Cholesterol absorption, ↑ LDL receptors	Elevated transaminases
Ezetimibe		10 mg daily	10 mg daily		
Bile acid sequestrants	Elevated LDL-C			↑ Bile acid excretion and ↑ LDL receptors	Bloating, constipation, elevated triglycerides
Cholestyramine		4 g daily	32 g daily		
Colestipol		5 g daily	40 g daily		
Colesevelam		3750 mg daily	4375 mg daily		
MTP inhibitor Lomitapide	HoFH	5 mg daily	60 mg daily	↓ VLDL production	Nausea, diarrhea, increased hepatic fat
ApoB inhibitor Mipomersen	HoFH	200 mg SC weekly	200 mg SC weekly	↓ VLDL production	Injection site reactions, flu-like symptoms, increased hepatic fat
Nicotinic acid Immediate-release Sustained-release Extended-release	Elevated LDL-C, elevated TG	100 mg tid 250 mg bid 500 mg qhs	1 g tid 1.5 g bid 2 g qhs	↓ VLDL production	Cutaneous flushing, GI upset, elevated glucose, uric acid, and elevated liver function tests
Fibric acid derivatives Gemfibrozil Fenofibrate	Elevated TG	600 mg bid 145 mg qd	600 mg bid 145 mg qd	↑ LPL, ↓ VLDL synthesis	Dyspepsia, myalgia, gallstones, elevated transaminases
Omega-3 fatty acids Omega-3 acid ethyl esters Icosapent ethyl	Elevated TG	4 g daily 4 g daily	4 g daily 4 g daily	↑ TG catabolism	Dyspepsia, fishy odor to breath

Abbreviations: GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein.

patients treated with any form of niacin. Niacin can raise plasma levels of uric acid and precipitate gouty attacks in susceptible patients. Acanthosis nigricans, a dark-colored coarse skin lesion, and maculopathy are infrequent side effects of niacin.

Management of Cholesterol to Prevent Cardiovascular Disease In contrast to hypertriglyceridemia and pancreatitis, there are abundant and compelling data that intervention to reduce LDL-C substantially reduces the risk of CVD, including myocardial infarction and stroke, as well as total mortality. Thus,

it is imperative that patients with hypercholesterolemia be assessed for cardiovascular risk and for the need for intervention. It is also worth noting that patients at high risk for CVD who have plasma LDL-C levels in the “normal” or average range also benefit from intervention to reduce LDL-C levels.

Lifestyle The first approach to a patient with hypercholesterolemia and high cardiovascular risk is to make any necessary lifestyle changes. In obese patients, efforts should be made to reduce body weight to the ideal level. Patients should receive dietary counseling to reduce the content of saturated fats, trans fats, and cholesterol in the diet. Regular aerobic exercise has relatively little impact on reducing plasma LDL-C levels, although it has cardiovascular benefits independent of LDL lowering.

Pharmacologic Therapy for Hypercholesterolemia The decision to use LDL-lowering drug therapy (Table 37-5)—with a statin being first-line therapy—depends on the level of LDL-C as well as the level of cardiovascular risk. In general, patients with a Mendelian disorder of elevated LDL-C such as FH must be treated to reduce the very high lifetime risk of CVD, and treatment should be initiated as early as possible in adulthood or, in some cases, during childhood.

Otherwise, the decision to initiate LDL-lowering drug therapy is generally determined by the level of cardiovascular risk. In patients with established CVD, statin therapy is well supported by clinical trial data and should be used regardless of the LDL-C level. For patients >40 years old without clinical CVD, the AHA/ACC risk calculator (http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp) can be used to determine the 10-year absolute risk for CVD, and current guidelines suggest that a 10-year risk >7.5% merits consideration of statin therapy regardless of plasma LDL-C level. For younger patients, the assessment of lifetime risk of CVD may help inform the decision to start a statin.

Hmg-coa reductase inhibitors (statins) Statins inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. By inhibiting cholesterol biosynthesis, statins lead to increased hepatic LDL receptor activity and accelerated clearance of circulating LDL, resulting in a dose-dependent reduction in plasma levels of LDL-C. The magnitude of LDL lowering associated with statin treatment varies widely among individuals, but once a patient is on a statin, the doubling of the statin dose produces an ~6% further reduction in the level of plasma LDL-C. The statins currently available differ in their LDL-C-reducing potency (Table 37-5). Currently, there is no convincing evidence that any of the different statins confer an advantage that is independent of the effect on LDL-C. Statins also reduce plasma TGs in a dose-dependent fashion, which is roughly proportional to their LDL-C-lowering effects (if the TGs are <400 mg/dL). Statins have a modest HDL-raising effect (5–10%) that is not generally dose-dependent.

Statins are well tolerated and can be taken in tablet form once a day. Potential side effects include dyspepsia, headaches, fatigue, and muscle or joint pains. Severe myopathy and even rhabdomyolysis occur rarely with statin treatment. The risk of statin-associated myopathy is increased by the presence of older age, frailty, renal insufficiency, and coadministration of drugs that interfere with the metabolism of statins, such as erythromycin and related antibiotics, antifungal agents, immunosuppressive drugs, and fibric acid derivatives (particularly gemfibrozil). Severe myopathy can usually be avoided by careful patient selection, avoidance of interacting drugs, and instructing the patient to contact the physician immediately in the event of unexplained muscle pain. In the event of muscle symptoms, the plasma creatine kinase (CK) level should be obtained to differentiate myopathy from myalgia. Serum CK levels need not be monitored on a routine basis in patients taking statins, because an elevated CK in the absence of symptoms does not predict the development of myopathy and does not necessarily suggest the need for discontinuing the drug.

Another consequence of statin therapy can be elevation in liver transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). They should be checked before starting therapy, at 2–3 months, and then annually. Substantial (greater than three times the upper limit of normal) elevation in transaminases is relatively rare, and mild-to-moderate (one to three times normal) elevation in transaminases in the absence of symptoms need not mandate discontinuing the medication. Severe clinical hepatitis associated with statins is exceedingly rare, and the trend is toward less frequent monitoring of transaminases in patients taking statins. The statin-associated elevation in liver enzymes resolves upon discontinuation of the medication.

Statins appear to be remarkably safe. Meta-analyses of large randomized controlled clinical trials with statins do not suggest an increase in any major noncardiac diseases except type 2 diabetes. A small excess percentage of those taking statins will develop diabetes but the benefits associated with the reduction in cardiovascular events outweigh the increase in incidence of diabetes. Statins are the drug class of choice for LDL-C reduction and are by far the most widely used class of lipid-lowering drugs.

Cholesterol absorption inhibitors Cholesterol within the lumen of the small intestine is derived from the diet (about one-third) and the bile (about two-thirds) and is actively absorbed by the enterocyte through a process that involves the protein NPC1L1. Ezetimibe (Table 37-5) is a cholesterol absorption inhibitor that binds directly to and inhibits NPC1L1 and blocks the intestinal absorption of cholesterol. Ezetimibe (10 mg) inhibits cholesterol absorption by almost 60%, resulting in a reduction in delivery of dietary sterols in the liver and an increase in hepatic LDL receptor expression. The mean reduction in plasma LDL-C on

ezetimibe (10 mg) is 18%, and the effect is additive when used in combination with a statin. Effects on TG and HDL-C levels are negligible. When used in combination with a statin, monitoring of liver transaminases is recommended. The only roles for ezetimibe in monotherapy are in patients who do not tolerate statins and in sitosterolemia.

Bile Acid Sequestrants (RESINS) Bile acid sequestrants bind bile acids in the intestine and promote their excretion rather than reabsorption in the ileum. To maintain the bile acid pool size, the liver diverts cholesterol to bile acid synthesis. The decreased hepatic intracellular cholesterol content results in upregulation of the LDL receptor and enhanced LDL clearance from the plasma. Bile acid sequestrants, including cholestyramine, colestipol, and colesevelam (Table 37-5), primarily reduce plasma LDL-C levels but can cause an increase in plasma TGs. Therefore, patients with hypertriglyceridemia generally should not be treated with bile acid-binding resins. Cholestyramine and colestipol are insoluble resins that must be suspended in liquids. Colesevelam is available as tablets but generally requires up to six to seven tablets per day for effective LDL-C lowering. Most side effects of resins are limited to the gastrointestinal tract and include bloating and constipation. Because bile acid sequestrants are not systemically absorbed, they are very safe and the cholesterol-lowering drug of choice in children and in women of childbearing age who are

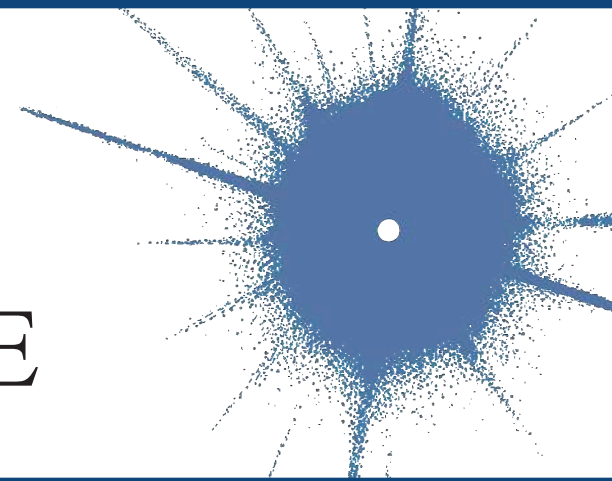
lactating, pregnant, or could become pregnant. They are effective in combination with statins and in combination with ezetimibe and are particularly useful with one or both of these drugs for patients with severe hypercholesterolemia or those with statin intolerance.

Specialized Drugs For Homozygous FH Two “orphan” drugs are approved specifically for the management of homozygous FH. They include a small-molecule inhibitor of MTP, called lomitapide, and an antisense oligonucleotide against apoB, called mipomersen. These drugs reduce VLDL production and LDL-C levels in homozygous FH patients. Due to their mechanism of action, each drug causes an increase in hepatic fat, the long-term consequences of which are unknown. In addition, lomitapide is associated with gastrointestinal-related side effects, and mipomersen is associated with skin reactions and flu-like symptoms.

LDL APHERESIS Patients who remain severely hypercholesterolemic despite optimally tolerated drug therapy are candidates for LDL apheresis. In this process, the patient's plasma is passed over a column that selectively removes the LDL, and the LDL-depleted plasma is returned to the patient. Patients on maximally tolerated combination drug therapy who have CHD and a plasma LDL-C level >200 mg/dL or no CHD and a plasma LDL-C level >300 mg/dL are candidates for every-other-week LDL apheresis and should be referred to a specialized lipid center.

CHAPTER 38

THE METABOLIC SYNDROME



Robert H. Eckel

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus. Evolution of the criteria for the metabolic syndrome since the original definition by the World Health Organization in 1998 reflects growing clinical evidence and analysis by a variety of consensus conferences and professional organizations. The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension ([Table 38-1](#)).

EPIDEMIOLOGY



The most challenging feature of the metabolic syndrome to define is waist circumference. Intraabdominal circumference (visceral adipose tissue) is considered most strongly related to insulin resistance and risk of diabetes and CVD, and for any given waist circumference the distribution of adipose tissue between SC and visceral depots varies substantially. Thus, within and between populations, there is a lesser vs. greater risk at the same waist circumference. These differences in populations are reflected in the range of waist circumferences considered to confer risk in different geographic locations ([Table 38-1](#)).

The prevalence of the metabolic syndrome varies around the world, in part reflecting the age and ethnicity of the populations studied and the diagnostic criteria applied. In general, the prevalence of the metabolic syndrome increases with age. The highest recorded prevalence worldwide is among Native Americans, with nearly 60% of women ages 45–49 and 45% of men ages 45–49 meeting the criteria of the National Cholesterol Education Program and Adult Treatment Panel III

(NCEP:ATPIII). In the United States, the metabolic syndrome is less common among African-American men and more common among Mexican-American women. Based on data from the National Health and Nutrition Examination Survey (NHANES) 2003–2006, the age-adjusted prevalence of the metabolic syndrome in U.S. adults without diabetes is 28% for men and 30% for women. In France, studies of a cohort of 30- to 60-year-olds have shown a <10% prevalence for each sex, although 17.5% of people 60–64 years of age are affected. Greater global industrialization is associated with rising rates of obesity, which are expected to increase the prevalence of the metabolic syndrome dramatically, especially as the population ages. Moreover, the rising prevalence and severity of obesity among children is reflected in features of the metabolic syndrome in a younger population.

The frequency distribution of the five components of the syndrome for the U.S. population (NHANES III) is summarized in [Fig. 38-1](#). Increases in waist circumference predominate among women, whereas increases in fasting plasma triglyceride levels (i.e., to >150 mg/dL), reductions in HDL cholesterol levels, and hyperglycemia are more likely in men.

RISK FACTORS

Overweight/obesity

Although the metabolic syndrome was first described in the early twentieth century, the worldwide overweight/obesity epidemic has recently been the force driving its increasing recognition. Central adiposity is a key feature of the syndrome, and the syndrome's prevalence reflects the strong relationship between waist circumference and increasing adiposity. However, despite the importance of obesity, patients who are of normal weight may also be insulin resistant and may have the metabolic syndrome.

NCEP:ATPIII^a 2001 AND HARMONIZING DEFINITION CRITERIA FOR THE METABOLIC SYNDROME

NCEP:ATPIII 2001	HARMONIZING DEFINITION ^b		
Three or more of the following: • Central obesity: waist circumference >102 cm (M), >88 cm (F) • Hypertriglyceridemia: triglyceride level ≥150 mg/dL or specific medication • Low HDL^c cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication • Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication • Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes	Three of the following: • Waist circumference (cm)		
	Men	Women	Ethnicity
	≥94	≥80	Europid, sub-Saharan African, Eastern and Middle Eastern
	≥90	≥80	South Asian, Chinese, and ethnic South and Central American
	≥85	≥90	Japanese
	• Fasting triglyceride level >150 mg/dL or specific medication • HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication • Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication • Fasting plasma glucose level ≥100 mg/dL (alternative indication: drug treatment of elevated glucose levels)		

^aNational Cholesterol Education Program and Adult Treatment Panel III.
^bIn this analysis, the following thresholds for waist circumference were used: white men, ≥94 cm; African-American men, ≥94 cm; Mexican-American men, ≥90 cm; white women, ≥80 cm; African-American women, ≥80 cm; Mexican-American women, ≥80 cm. For participants whose designation was “other race—including multiracial,” thresholds that were once based on Europid cutoffs (≥94 cm for men and ≥80 cm for women) and on South Asian cutoffs (≥90 cm for men and ≥80 cm for women) were used. For participants who were considered “other Hispanic,” the International Diabetes Federation thresholds for ethnic South and Central Americans were used.
^cHigh-density lipoprotein.

Sedentary lifestyle

Physical inactivity is a predictor of CVD events and the related risk of death. Many components of the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central), reduced HDL cholesterol, and increased triglycerides, blood pressure, and glucose in genetically susceptible persons. Compared with individuals who watch television or videos or use the computer <1 h daily, those who do so for >4 h daily have a two-fold increased risk of the metabolic syndrome.

Aging

The metabolic syndrome affects nearly 50% of the U.S. population older than age 50, and at >60 years of age women are more often affected than men. The age dependency of the syndrome’s prevalence is seen in most populations around the world.

Diabetes mellitus

Diabetes mellitus is included in both the NCEP and the harmonizing definitions of the metabolic syndrome. It is estimated that the great majority (~75%) of patients with type 2 diabetes or impaired glucose tolerance have the metabolic syndrome. The presence of the metabolic syndrome in these populations relates to a higher

prevalence of CVD than in patients who have type 2 diabetes or impaired glucose tolerance but do not have this syndrome.

Cardiovascular disease

Individuals with the metabolic syndrome are twice as likely to die of cardiovascular disease as those who do not, and their risk of an acute myocardial infarction or stroke is threefold higher. The approximate prevalence of the metabolic syndrome among patients with coronary heart disease (CHD) is 50%, with a prevalence of ~35% among patients with premature coronary artery disease (before or at age 45) and a particularly high prevalence among women. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., nutrition, physical activity, weight reduction, and—in some cases—pharmacologic therapy), the prevalence of the syndrome can be reduced.

Lipodystrophy

Lipodystrophic disorders in general are associated with the metabolic syndrome. Both genetic lipodystrophy (e.g., Berardinelli-Seip congenital lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired lipodystrophy (e.g., HIV-related lipodystrophy in patients receiving antiretroviral therapy) may give rise to severe insulin resistance and many of the components of the metabolic syndrome.

ETIOLOGY

Insulin resistance

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, which is caused by an incompletely understood defect in insulin action. The onset of insulin resistance is heralded by postprandial hyperinsulinemia, which is followed by fasting hyperinsulinemia and ultimately by hyperglycemia.

An early major contributor to the development of insulin resistance is an overabundance of circulating fatty acids (**Fig. 38-2**). Plasma albumin-bound free fatty acids are derived predominantly from adipose-tissue triglyceride stores released by intracellular lipolytic enzymes. Fatty acids are also derived from the lipolysis of triglyceride-rich lipoproteins in tissues by lipoprotein lipase. Insulin mediates both antilipolysis and the stimulation of lipoprotein lipase in adipose tissue. Of note, the inhibition of lipolysis in adipose tissue is the most sensitive pathway of insulin action. Thus, when insulin resistance develops, increased lipolysis produces more fatty acids, which further decrease the antilipolytic effect of insulin. Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signaling. Fatty acids impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle, whereas increased glucose production and triglyceride accumulation take place in the liver.

Leptin resistance has also been raised as a possible pathophysiologic mechanism to explain the metabolic syndrome. Physiologically, leptin reduces appetite,

promotes energy expenditure, and enhances insulin sensitivity. In addition, leptin may regulate cardiac and vascular function through a nitric oxide-dependent mechanism. However, when obesity develops, hyperleptinemia ensues, with evidence of leptin resistance in the brain and other tissues resulting in inflammation, insulin resistance, hyperlipidemia, and a plethora of cardiovascular disorders, such as hypertension, atherosclerosis, CHD, and heart failure.

The oxidative stress hypothesis provides a unifying theory for aging and the predisposition to the metabolic syndrome. In studies of insulin-resistant individuals with obesity or type 2 diabetes, the offspring of patients with type 2 diabetes, and the elderly, a defect in mitochondrial oxidative phosphorylation that leads to the accumulation of triglycerides and related lipid molecules in muscle has been identified.

Recently, the gut microbiome has emerged as an important contributor to the development of obesity and related metabolic disorders, including the metabolic syndrome. Although the mechanism remains uncertain, interaction among genetic predisposition, diet, and the intestinal flora is important.

Increased waist circumference

Waist circumference is an important component of the most recent and frequently applied diagnostic criteria for the metabolic syndrome. However, measuring waist circumference does not reliably distinguish increases in SC adipose tissue from those in visceral fat; this distinction requires CT or MRI. With increases in visceral adipose tissue, adipose tissue-derived free fatty acids are directed to the liver. In contrast, increases in abdominal SC fat release lipolysis products into the systemic circulation and avert more direct effects on hepatic metabolism. Relative increases in visceral versus SC adipose tissue with increasing waist circumference in Asians and Asian Indians may explain the greater prevalence of the syndrome in those populations than in African-American men, in whom SC fat predominates. It is also possible that visceral fat is a marker for—but not the source of—excess postprandial free fatty acids in obesity.

Dyslipidemia

In general, free fatty acid flux to the liver is associated with increased production of ApoB-containing, triglyceride-rich, very low-density lipoproteins (VLDLs) (**see also Chap. 37**). The effect of insulin on this process is complex, but hypertriglyceridemia is an excellent marker of the insulin-resistant condition. Not only is hypertriglyceridemia a feature of the metabolic syndrome, but patients with the metabolic syndrome have elevated levels of ApoCIII carried on VLDLs and other lipoproteins. This increase in ApoCIII is inhibitory to

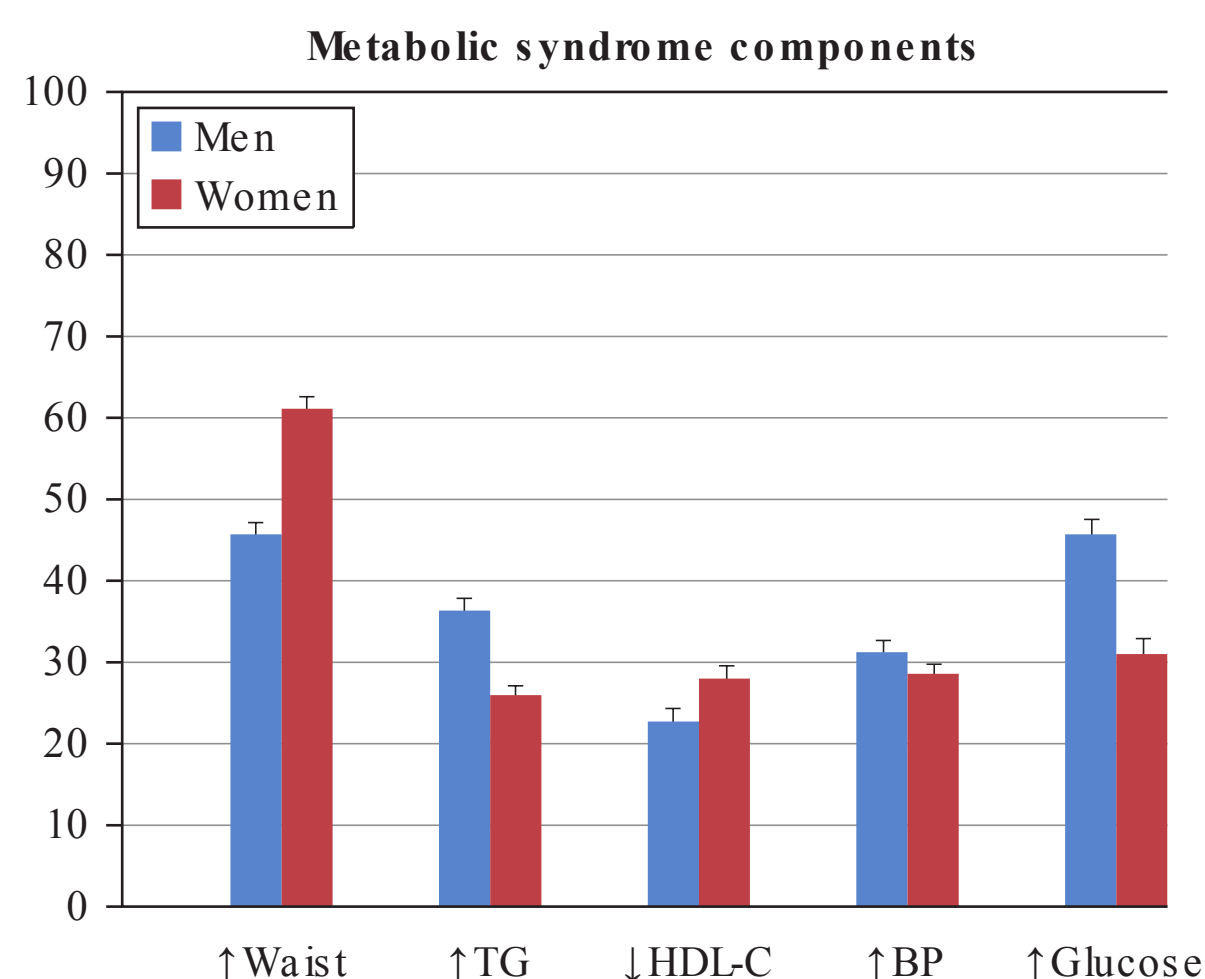


FIGURE 38-1

Prevalence of the metabolic syndrome components, from NHANES 2003–2006. NHANES, National Health and Nutrition Examination Survey; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure. The prevalence of elevated glucose includes individuals with known diabetes mellitus. (Created from data in ES Ford et al: *J Diabetes* 2:1753, 2010.)

lipoprotein lipase, further contributing to hypertriglyceridemia and also associated with more atherosclerotic cardiovascular disease.

The other major lipoprotein disturbance in the metabolic syndrome is a reduction in HDL cholesterol. This reduction is a consequence of changes in HDL composition and metabolism. In the presence of hypertriglyceridemia, a decrease in the cholesterol content of HDL is a consequence of reduced cholesteryl ester content of the lipoprotein core in combination with cholesteryl ester transfer protein-mediated alterations in triglyceride that make the particle small and dense. This change in lipoprotein composition also results in increased clearance of HDL from the circulation. These changes in HDL have a relationship to insulin resistance that is probably indirect, occurring in concert with the changes in triglyceride-rich lipoprotein metabolism.

In addition to HDLs, low-density lipoproteins (LDLs) are modified in composition in the metabolic syndrome. With fasting serum triglycerides at >2.0 mM (~ 180 mg/dL), there is almost always a predominance of small, dense LDLs, which are thought to be more atherogenic although their association with hypertriglyceridemia and low HDLs make their independent contribution to CVD events difficult to assess. Individuals with hypertriglyceridemia often have increases in cholesterol content of both VLDL1 and VLDL2 subfractions and in LDL particle number. Both of these lipoprotein changes may contribute to atherogenic risk in patients with the metabolic syndrome.

Glucose intolerance

Defects in insulin action in the metabolic syndrome lead to impaired suppression of glucose production by the liver and kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues—i.e., muscle and adipose tissue. The relationship between impaired fasting glucose or impaired glucose tolerance and insulin resistance is well supported by studies of humans, nonhuman primates, and rodents. To compensate for defects in insulin action, insulin secretion and/or clearance must be modified so that euglycemia is sustained. Ultimately, this compensatory mechanism fails, usually because of defects in insulin secretion, resulting in progression from impaired fasting glucose and/or impaired glucose tolerance to diabetes mellitus.

Hypertension

The relationship between insulin resistance and hypertension is well established. Paradoxically, under normal physiologic conditions, insulin is a vasodilator with secondary effects on sodium reabsorption in the kidney. However, in the setting of insulin resistance, the

vasodilatory effect of insulin is lost but the renal effect on sodium reabsorption is preserved. Sodium reabsorption is increased in whites with the metabolic syndrome but not in Africans or Asians. Insulin also increases the activity of the sympathetic nervous system, an effect that may be preserved in the setting of insulin resistance. Insulin resistance is characterized by pathway-specific impairment in phosphatidylinositol-3-kinase signaling. In the endothelium, this impairment may cause an imbalance between the production of nitric oxide and the secretion of endothelin 1, with a consequent decrease in blood flow. Although these mechanisms are provocative, evaluation of insulin action by measurement of fasting insulin levels or by homeostasis model assessment shows that insulin resistance contributes only partially to the increased prevalence of hypertension in the metabolic syndrome.

Another possible mechanism underlying hypertension in the metabolic syndrome is the vasoactive role of perivascular adipose tissue. Reactive oxygen species released by NADPH oxidase impair endothelial function and result in local vasoconstriction. Other paracrine effects could be mediated by leptin or other proinflammatory cytokines released from adipose tissue, such as tumor necrosis factor α .

Hyperuricemia is another consequence of insulin resistance and is commonly observed in the metabolic syndrome. There is growing evidence not only that uric acid is associated with hypertension but also that reduction of uric acid normalizes blood pressure in hyperuricemic adolescents with hypertension. The mechanism appears to be related to an adverse effect of uric acid on nitric acid synthase in the macula densa of the kidney and stimulation of the renin-angiotensin aldosterone system.

Proinflammatory cytokines

The increases in proinflammatory cytokines—including interleukins 1, 6, and 18; resistin; tumor necrosis factor α ; and the systemic biomarker C-reactive protein—reflect overproduction by the expanded adipose tissue mass (Fig. 38-2). Adipose tissue-derived macrophages may be the primary source of proinflammatory cytokines locally and in the systemic circulation. It remains unclear, however, how much of the insulin resistance is caused by the paracrine effects of these cytokines and how much by the endocrine effects.

Adiponectin

Adiponectin is an anti-inflammatory cytokine produced exclusively by adipocytes. Adiponectin enhances insulin sensitivity and inhibits many steps in the inflammatory process. In the liver, adiponectin inhibits the expression of gluconeogenic enzymes and the rate

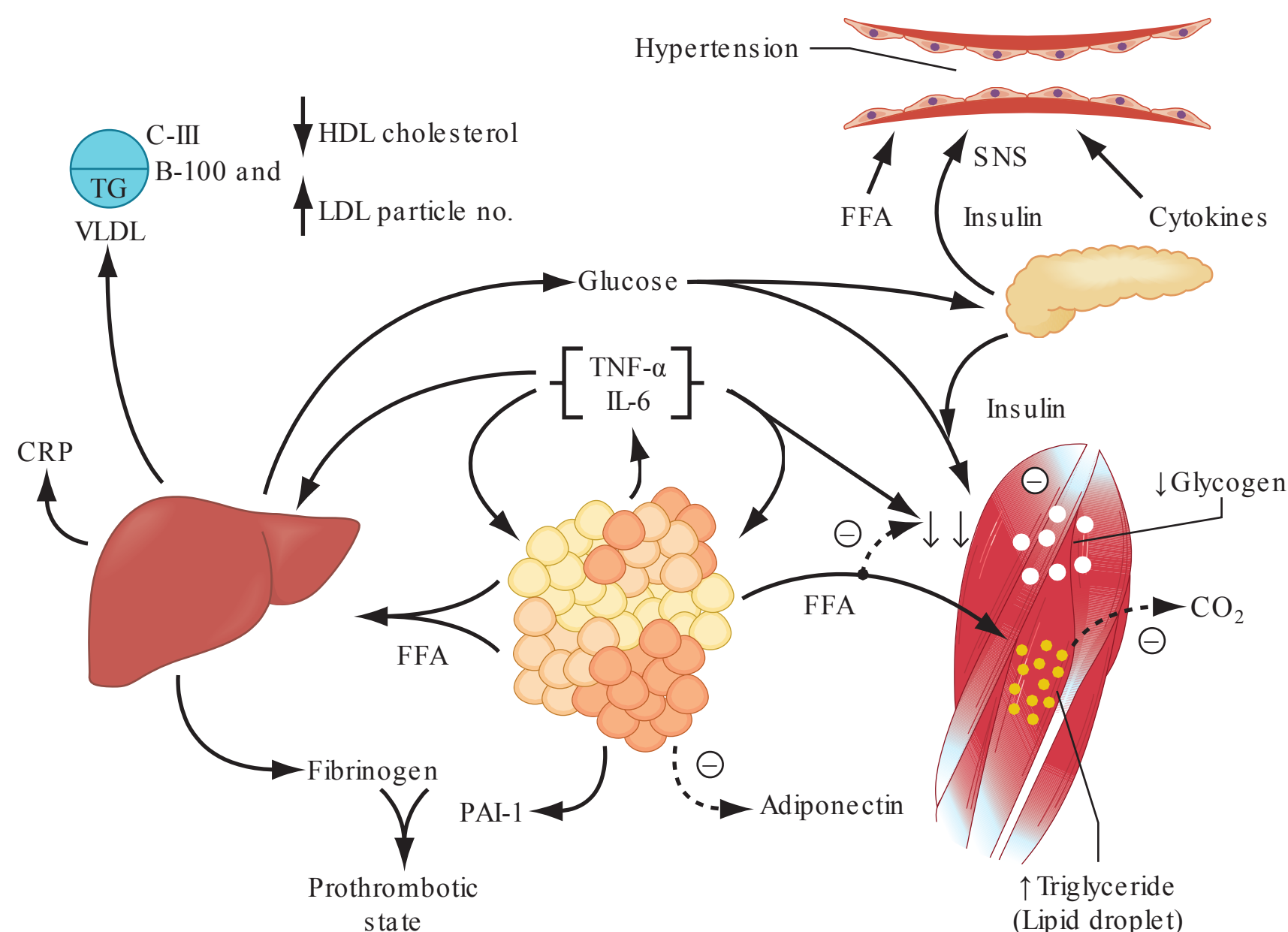


FIGURE 38-2

Pathophysiology of the metabolic syndrome. Free fatty acids (FFAs) are released in abundance from an expanded adipose tissue mass. In the liver, FFAs result in increased production of glucose and triglycerides and secretion of very low density lipoproteins (VLDLs). Associated lipid/lipoprotein abnormalities include reductions in high-density lipoprotein (HDL) cholesterol and an increased low-density lipoprotein (LDL) particle number (no.). FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride (TG). The increase in circulating glucose, and to some extent FFAs, increases pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to hypertension, as might higher levels of circulating

FFAs. The proinflammatory state is superimposed and contributory to the insulin resistance produced by excessive FFAs. The enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α) produced by adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFAs. IL-6 and other cytokines also enhance hepatic glucose production, VLDL production by the liver, hypertension and insulin resistance in muscle. Cytokines and FFAs also increase hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1), resulting in a prothrombotic state. Higher levels of circulating cytokines stimulate hepatic production of C-reactive protein (CRP). Reduced production of the anti-inflammatory and insulin-sensitizing cytokine adiponectin is also associated with the metabolic syndrome. (Modified from RH Eckel et al: Lancet 365:1415, 2005.)

of glucose production. In muscle, adiponectin increases glucose transport and enhances fatty acid oxidation, partially through the activation of AMP kinase. Adiponectin levels are reduced in the metabolic syndrome. The relative contributions of adiponectin deficiency and overabundance of the proinflammatory cytokines are unclear.

CLINICAL FEATURES

Symptoms and signs

The metabolic syndrome typically is not associated with symptoms. On physical examination, waist circumference may be expanded and blood pressure elevated. The presence of either or both of these signs should prompt the clinician to search for other biochemical abnormalities that may be associated with the metabolic syndrome. Less frequently, lipoatrophy or acanthosis

nigricans is found on examination. Because these physical findings characteristically are associated with severe insulin resistance, other components of the metabolic syndrome should be expected.

Associated diseases

Cardiovascular disease

The relative risk for new-onset CVD in patients with the metabolic syndrome who do not have diabetes averages 1.5–3 fold. However, an 8-year follow-up of middle-aged participants in the Framingham Offspring Study documented that the population-attributable CVD risk in the metabolic syndrome was 34% among men and only 16% among women. In the same study, both the metabolic syndrome and diabetes predicted ischemic stroke, with greater risk among patients with the metabolic syndrome than among those with diabetes alone (19% vs. 7%) and a particularly large difference among

women (27% vs. 5%). Patients with the metabolic syndrome are also at increased risk for peripheral vascular disease.

■ Type 2 diabetes

Overall, the risk for type 2 diabetes among patients with the metabolic syndrome is increased three- to fivefold. In the Framingham Offspring Study's 8-year follow-up of middle-aged participants, the population-attributable risk for developing type 2 diabetes was 62% among men and 47% among women.

Other associated conditions

In addition to the features specifically associated with the metabolic syndrome, other metabolic alterations accompany insulin resistance. These alterations include increases in ApoB and ApoCIII, uric acid, prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1), serum viscosity, asymmetric dimethylarginine, homocysteine, white blood cell count, proinflammatory cytokines, C-reactive protein, microalbuminuria, non-alcoholic fatty liver disease and/or nonalcoholic steatohepatitis, polycystic ovary syndrome, and obstructive sleep apnea.

■ Nonalcoholic fatty liver disease

Fatty liver is a relatively common condition, affecting 25–45% of the U.S. population. However, in nonalcoholic steatohepatitis, triglyceride accumulation and inflammation coexist. Nonalcoholic steatohepatitis is now present in 3–12% of the population of the United States and other Western countries. Of patients with the metabolic syndrome, ~25–60% have nonalcoholic fatty liver disease and up to 35% have nonalcoholic steatohepatitis. As the prevalence of overweight/obesity and the metabolic syndrome increases, nonalcoholic steatohepatitis may become one of the more common causes of end-stage liver disease and hepatocellular carcinoma.

■ Hyperuricemia

Hyperuricemia reflects defects in insulin action on the renal tubular reabsorption of uric acid and may contribute to hypertension through its effect on the endothelium. An increase in asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, also relates to endothelial dysfunction. In addition, microalbuminuria may be caused by altered endothelial pathophysiology in the insulin-resistant state.

■ Polycystic ovary syndrome

Polycystic ovary syndrome is highly associated with insulin resistance (50–80%) and the metabolic syndrome, with a prevalence of the syndrome between 40% and 50%. Women with polycystic ovary syndrome are two to four times more likely to have the metabolic

syndrome than are women without polycystic ovary syndrome.

■ Obstructive sleep apnea

Obstructive sleep apnea is commonly associated with obesity, hypertension, increased circulating cytokines, impaired glucose tolerance, and insulin resistance. With these associations, it is not surprising that individuals with obstructive sleep apnea frequently have the metabolic syndrome. Moreover, when biomarkers of insulin resistance are compared between patients with obstructive sleep apnea and weight-matched controls, insulin resistance is found to be more severe in those with apnea. Continuous positive airway pressure treatment improves insulin sensitivity in patients with obstructive sleep apnea.

DIAGNOSIS

The diagnosis of the metabolic syndrome relies on fulfillment of the criteria listed in Table 38-1, as assessed using tools at the bedside and in the laboratory. The medical history should include evaluation of symptoms for obstructive sleep apnea in all patients and polycystic ovary syndrome in premenopausal women. Family history will help determine risk for CVD and diabetes mellitus. Blood pressure and waist circumference measurements provide information necessary for the diagnosis.

Laboratory tests

Measurement of fasting lipids and glucose is needed in determining whether the metabolic syndrome is present. The measurement of additional biomarkers associated with insulin resistance can be individualized. Such tests might include those for ApoB, high-sensitivity C-reactive protein, fibrinogen, uric acid, urinary microalbumin, and liver function. A sleep study should be performed if symptoms of obstructive sleep apnea are present. If polycystic ovary syndrome is suspected on the basis of clinical features and anovulation, testosterone, luteinizing hormone, and follicle-stimulating hormone should be measured.

TREATMENT The Metabolic Syndrome

LIFESTYLE Obesity is the driving force behind the metabolic syndrome. Thus, weight reduction is the primary approach to the disorder. With weight reduction, improvement in insulin sensitivity is often accompanied by favorable modifications in many components of the metabolic syndrome. In general, recommendations for weight loss include a combination of caloric restriction, increased physical activity, and behavior

modification. Caloric restriction is the most important component, whereas increases in physical activity are important for maintenance of weight loss. Some but not all evidence suggests that the addition of exercise to caloric restriction may promote greater weight loss from the visceral depot. The tendency for weight regain after successful weight reduction underscores the need for long-lasting behavioral changes.

Diet Before prescribing a weight-loss diet, it is important to emphasize that it has taken the patient a long time to develop an expanded fat mass; thus, the correction need not occur quickly. Given that ~ 3500 kcal = 1 lb of fat, ~ 500 -kcal restriction daily equates to weight reduction of 1 lb per week. Diets restricted in carbohydrate typically provide a rapid initial weight loss. However, after 1 year, the amount of weight reduction is minimally reduced or no different from that with caloric restriction alone. Thus, adherence to the diet is more important than which diet is chosen. Moreover, there is concern about low-carbohydrate diets enriched in saturated fat, particularly for patients at risk for CVD. Therefore, a high-quality dietary pattern—i.e., a diet enriched in fruits, vegetables, whole grains, lean poultry, and fish—should be encouraged to maximize overall health benefit.

Physical Activity Before a physical activity recommendation is provided to patients with the metabolic syndrome, it is important to ensure that the increased activity does not incur risk. Some high-risk patients should undergo formal cardiovascular evaluation before initiating an exercise program. For an inactive participant, gradual increases in physical activity should be encouraged to enhance adherence and avoid injury. Although increases in physical activity can lead to modest weight reduction, 60–90 min of daily activity is required to achieve this goal. Even if an overweight or obese adult is unable to undertake this level of activity, a significant health benefit will follow from at least 30 min of moderate-intensity activity daily. The caloric value of 30 min of a variety of activities can be found at www.heart.org/HEARTORG/GettingHealthy/WeightManagement/LosingWeight/LosingWeight_UCM_307904_Article.jsp. Of note, a variety of routine activities, such as gardening, walking, and housecleaning, require moderate caloric expenditure. Thus, physical activity need not be defined solely in terms of formal exercise such as jogging, swimming, or tennis.

Behavior Modification Behavioral treatment typically includes recommendations for dietary restriction and more physical activity, resulting in weight loss that benefits metabolic health. The subsequent challenge is the duration of the program because weight regain so often follows successful weight reduction. Long-term outcomes may be enhanced by a variety of methods, such as the Internet, social media, and telephone follow-up to maintain contact between providers and patients.

Obesity In some patients with the metabolic syndrome, treatment options need to extend beyond lifestyle intervention. Weight-loss drugs come in two major classes: appetite suppressants and absorption inhibitors. Appetite suppressants

approved by the U.S. Food and Drug Administration include phentermine (for short-term use [3 months] only) as well as the more recent additions phentermine/topiramate and lorcaserin, which are approved without restrictions on the duration of therapy. In clinical trials, the phentermine/topiramate combination has resulted in $\sim 10\%$ weight loss in 50% of patients. Side effects include palpitations, headache, paresthesias, constipation, and insomnia. Lorcaserin results in less weight loss—typically $\sim 5\%$ beyond placebo—but can cause headache and nasopharyngitis. Orlistat inhibits fat absorption by $\sim 30\%$ and is moderately effective compared with placebo ($\sim 5\%$ more weight loss). Orlistat has been shown to reduce the incidence of type 2 diabetes, an effect that was especially evident among patients with impaired glucose tolerance at baseline. This drug is often difficult to take because of oily leakage per rectum.

Metabolic or bariatric surgery is an option for patients with the metabolic syndrome who have a body mass index >40 kg/m², or >35 kg/m² with comorbidities. An evolving application for metabolic surgery includes patients with a body mass index as low as 30 kg/m² and type 2 diabetes. Gastric bypass or vertical sleeve gastrectomy results in dramatic weight reduction and improvement in the features of the metabolic syndrome. A survival benefit with gastric bypass has also been realized.

LDL CHOLESTEROL The rationale for the NCEP:ATPIII's development of criteria for the metabolic syndrome was to go beyond LDL cholesterol in identifying and reducing the risk of CVD (see also Chap. 37). The working assumption by the panel was that LDL cholesterol goals had already been achieved and that increasing evidence supports a linear reduction in CVD events as a result of progressive lowering of LDL cholesterol with statins. For patients with the metabolic syndrome and diabetes, a statin should be prescribed. For those patients with diabetes and known CVD, the current evidence supports a maximum of penultimate dose of a potent statin (e.g., atorvastatin or rosuvastatin). For those patients with the metabolic syndrome but without diabetes, a score that predicts a 10-year CVD risk exceeding 7.5% should also take a statin. With a 10-year risk of $<7.5\%$, use of statin therapy is not evidence based.

Diets restricted in saturated fats ($<7\%$ of calories) and trans-fats (as few as possible) should be applied aggressively. Although less evidence exists, dietary cholesterol should also be restricted. If LDL cholesterol remains elevated, pharmacologic intervention is needed. Treatment with statins, which lower LDL cholesterol by 15–60%, is evidence based and is the first-choice medication intervention. Of note, for each doubling of the statin dose, LDL cholesterol is further lowered by only $\sim 6\%$. Hepatotoxicity (more than a threefold increase in hepatic aminotransferases) is rare, and myopathy is seen in $\sim 10\%$ of patients. The cholesterol absorption inhibitor ezetimibe is well tolerated and should be the second-choice medication intervention. Ezetimibe typically reduces LDL cholesterol by 15–20%. The bile acid sequestrants

cholestyramine, colestipol, and colesevalam may be more effective than ezetimibe but, because they can increase triglyceride levels, must be used with caution in patients with the metabolic syndrome. In general, bile sequestrants should not be administered when fasting triglyceride levels are >250 mg/dL. Side effects include gastrointestinal symptoms (palatability, bloating, belching, constipation, anal irritation). Nicotinic acid has modest LDL cholesterol-lowering capabilities ($<20\%$). Fibrates are best employed to lower LDL cholesterol when both LDL cholesterol and triglycerides are elevated. Fenofibrate may be more effective than gemfibrozil in this setting.

TRIGLYCERIDES The NCEP:ATPIII has focused on non-HDL cholesterol rather than on triglycerides (see also Chap. 37). However, a fasting triglyceride value of <150 mg/dL is recommended. In general, the response of fasting triglycerides relates to the amount of weight reduction achieved: a weight reduction of $>10\%$ is necessary to lower fasting triglyceride levels.

A fibrate (gemfibrozil or fenofibrate) is the drug of choice to lower fasting triglyceride levels, which are typically reduced by 30–45%. Concomitant administration with drugs metabolized by the 3A4 cytochrome P450 system (including some statins) increases the risk of myopathy. In these cases, fenofibrate may be preferable to gemfibrozil. In the Veterans Affairs HDL Intervention Trial, gemfibrozil was administered to men with known CHD and levels of HDL cholesterol <40 mg/dL. A coronary disease event and mortality rate benefit was experienced predominantly among men with hyperinsulinemia and/or diabetes, many of whom were identified retrospectively as having the metabolic syndrome. Of note, the degree of triglyceride lowering in this trial did not predict benefit. Although levels of LDL cholesterol did not change, a decrease in LDL particle number correlated with benefit. Several additional clinical trials have not shown clear evidence that fibrates reduce CVD risk; however, post hoc analyses of several studies demonstrated that patients with baseline triglyceride levels >200 mg/dL and HDL cholesterol levels <35 mg/dL did benefit.

Other drugs that lower triglyceride levels include statins, nicotinic acid, and—in high doses—omega-3 fatty acids. For this purpose, an intermediate or high dose of the “more potent” statins (atorvastatin, rosuvastatin) is needed. The effect of nicotinic acid on fasting triglycerides is dose related and ~ 20 – 35% , an effect that is less pronounced than that of fibrates. In patients with the metabolic syndrome and diabetes, nicotinic acid may increase fasting glucose levels. Omega-3 fatty acid preparations that include high doses of docosahexaenoic acid plus eicosapentaenoic acid (~ 1.5 – 4.5 g/d) or eicosapentaenoic acid alone lower fasting triglyceride levels by ~ 30 – 40% . No drug interactions with fibrates or statins occur, and the main side effect of their use is eructation with a fishy taste. This taste can be partially blocked by ingestion of the nutraceutical after freezing. Clinical trials of

nicotinic acid or high-dose omega-3 fatty acids in patients with the metabolic syndrome have not been reported.

HDL CHOLESTEROL Very few lipid-modifying compounds increase HDL cholesterol levels (see also Chap. 37). Statins, fibrates, and bile acid sequestrants have modest effects (5–10%), whereas ezetimibe and omega-3 fatty acids have no effect. Nicotinic acid is the only currently available drug with predictable HDL cholesterol-raising properties. The response is dose related, and nicotinic acid can increase HDL cholesterol by $\sim 30\%$ above baseline. After several trials of nicotinic acid versus placebo in statin-treated patients, there is still no evidence that raising HDL with nicotinic acid beneficially affects CVD events in patients with or without the metabolic syndrome.

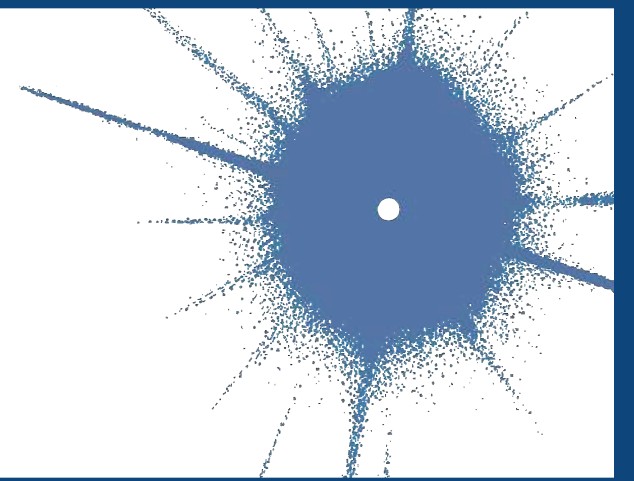
BLOODPRESSURE The direct relationship between blood pressure and all-cause mortality rate has been well established in studies comparing patients with hypertension ($>140/90$ mmHg), patients with pre-hypertension ($>120/80$ mmHg but $<140/90$ mmHg), and individuals with normal blood pressure ($<120/80$ mmHg) (see also Chap. 43). In patients who have the metabolic syndrome without diabetes, the best choice for the initial antihypertensive medication is an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker, as these two classes of drugs appear to reduce the incidence of new-onset type 2 diabetes. In all patients with hypertension, a sodium-restricted dietary pattern enriched in fruits and vegetables, whole grains, and low-fat dairy products should be advocated. Home monitoring of blood pressure may assist in maintaining good blood-pressure control.

IMPAIRED FASTING GLUCOSE In patients with the metabolic syndrome and type 2 diabetes, aggressive glycemic control may favorably modify fasting levels of triglycerides and/or HDL cholesterol. In patients with impaired fasting glucose who do not have diabetes, a lifestyle intervention that includes weight reduction, dietary fat restriction, and increased physical activity has been shown to reduce the incidence of type 2 diabetes. Metformin also reduces the incidence of diabetes, although the effect is less pronounced than that of lifestyle intervention.

INSULIN RESISTANCE Several drug classes (biguanides, thiazolidinediones [TZDs]) increase insulin sensitivity. Because insulin resistance is the primary pathophysiologic mechanism for the metabolic syndrome, representative drugs in these classes reduce its prevalence. Both metformin and TZDs enhance insulin action in the liver and suppress endogenous glucose production. TZDs, but not metformin, also improve insulin-mediated glucose uptake in muscle and adipose tissue. Benefits of both drugs have been seen in patients with nonalcoholic fatty liver disease and polycystic ovary syndrome, and the drugs have been shown to reduce markers of inflammation.

CHAPTER 39

ISCHEMIC HEART DISEASE



Elliott M. Antman ■ Joseph Loscalzo

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery. **Chapter 36** deals with the development and treatment of atherosclerosis. This chapter focuses on the chronic manifestations and treatment of IHD. The subsequent chapters address the acute phases of IHD.

EPIDEMIOLOGY AND GLOBAL TRENDS



IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. IHD is the most common, serious, chronic, life-threatening illness in the United States, where 13 million persons have IHD, >6 million have angina pectoris, and >7 million have sustained a myocardial infarction. Genetic factors, a high-fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD (**Chap. 36**). In the United States and Western Europe, IHD is growing among low-income groups, but primary prevention has delayed the disease to later in life in all socioeconomic groups. Despite these sobering statistics, it is worth noting that epidemiologic data show a decline in the rate of deaths due to IHD, about half of which is attributable to treatments and half to prevention by risk factor modification.

Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD. These trends are occurring in the general context of population growth and as a result of the increase in the average age of the world's population. With

urbanization in countries with emerging economies and a growing middle class, elements of the energy-rich Western diet are being adopted. As a result, the prevalence of risk factors for IHD and the prevalence of IHD itself are both increasing rapidly, so that in analyses of the global burden of disease, there is a shift from communicable to noncommunicable diseases. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India and the Middle East. In light of the projection of large increases in IHD throughout the world, IHD is likely to become the most common cause of death worldwide by 2020.

PATHOPHYSIOLOGY

Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. In normal conditions, for any given level of a demand for oxygen, the myocardium will control the supply of oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction. The major determinants of myocardial oxygen demand (MVO_2) are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood flow. Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries: (1) large epicardial arteries ($Resistance\ 1 = R_1$), (2) prearteriolar vessels (R_2), and (3) arteriolar and intramyocardial capillary vessels (R_3). In the absence of significant flow-limiting atherosclerotic obstructions, R_1 is trivial; the major determinant of coronary resistance is found in R_2 and R_3 .

The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate a great capacity for dilation (R_2 and R_3 decrease). For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and in this manner regulate the supply of oxygen and substrate to the myocardium (metabolic regulation). The coronary resistance vessels also adapt to physiologic alterations in blood pressure to maintain coronary blood flow at levels appropriate to myocardial needs (autoregulation).

By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow also can be limited by spasm (see Prinzmetal's angina in **Chap. 40**), arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities such as the origin of the left anterior descending coronary artery from the pulmonary artery may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults.

Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased and particularly when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely owing to subendocardial ischemia (**Chap. 23**). A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself but may lower the threshold for ischemia in patients with moderate coronary obstruction.

Not infrequently, two or more causes of ischemia coexist in a patient, such as an increase in oxygen demand due to left ventricular hypertrophy secondary to hypertension and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia. Abnormal constriction or failure of normal dilation of the coronary resistance vessels also can cause ischemia. When it causes angina, this condition is referred to as microvascular angina.

CORONARY ATHEROSCLEROSIS

Epicardial coronary arteries are the major site of atherosclerotic disease. The major risk factors for atherosclerosis (high levels of plasma low-density lipoprotein

[LDL], low plasma high-density lipoprotein [HDL], cigarette smoking, hypertension, and diabetes mellitus [**Chap. 36**]) disturb the normal functions of the vascular endothelium. These functions include local control of vascular tone, maintenance of an antithrombotic surface, and control of inflammatory cell adhesion and diapedesis. The loss of these defenses leads to inappropriate constriction, luminal thrombus formation, and abnormal interactions between blood cells, especially monocytes and platelets, and the activated vascular endothelium. Functional changes in the vascular milieu ultimately result in the subintimal collections of fat, smooth muscle cells, fibroblasts, and intercellular matrix that define the atherosclerotic plaque. Rather than viewing atherosclerosis strictly as a vascular problem, it is useful to consider it in the context of alterations in the nature of the circulating blood (hyperglycemia; increased concentrations of LDL cholesterol, tissue factor, fibrinogen, von Willebrand factor, coagulation factor VII, and platelet microparticles). The combination of a "vulnerable vessel" in a patient with "vulnerable blood" promotes a state of hypercoagulability and hypofibrinolysis. This is especially true in patients with diabetes mellitus.

Atherosclerosis develops at irregular rates in different segments of the epicardial coronary tree and leads eventually to segmental reductions in cross-sectional area, i.e., plaque formation. There is also a predilection for atherosclerotic plaques to develop at sites of increased turbulence in coronary flow, such as at branch points in the epicardial arteries. When a stenosis reduces the diameter of an epicardial artery by 50%, there is a limitation of the ability to increase flow to meet increased myocardial demand. When the diameter is reduced by ~80%, blood flow at rest may be reduced, and further minor decreases in the stenotic orifice area can reduce coronary flow dramatically to cause myocardial ischemia at rest or with minimal stress.

Segmental atherosclerotic narrowing of epicardial coronary arteries is caused most commonly by the formation of a plaque, which is subject to rupture or erosion of the cap separating the plaque from the bloodstream. Upon exposure of the plaque contents to blood, two important and interrelated processes are set in motion: (1) platelets are activated and aggregate, and (2) the coagulation cascade is activated, leading to deposition of fibrin strands. A thrombus composed of platelet aggregates and fibrin strands traps red blood cells and can reduce coronary blood flow, leading to the clinical manifestations of myocardial ischemia.

The location of the obstruction influences the quantity of myocardium rendered ischemic and determines the severity of the clinical manifestations. Thus, critical obstructions in vessels, such as the left main coronary

artery and the proximal left anterior descending coronary artery, are particularly hazardous. Chronic severe coronary narrowing and myocardial ischemia frequently are accompanied by the development of collateral vessels, especially when the narrowing develops gradually. When well developed, such vessels can by themselves provide sufficient blood flow to sustain the viability of the myocardium at rest but not during conditions of increased demand.

With progressive worsening of a stenosis in a proximal epicardial artery, the distal resistance vessels (when they function normally) dilate to reduce vascular resistance and maintain coronary blood flow. A pressure gradient develops across the proximal stenosis, and poststenotic pressure falls. When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction. In these circumstances, ischemia, manifest clinically by angina or electrocardiographically by ST-segment deviation, can be precipitated by increases in myocardial oxygen demand caused by physical activity, emotional stress, and/or tachycardia. Changes in the caliber of the stenosed coronary artery due to physiologic vasomotion, loss of endothelial control of dilation (as occurs in atherosclerosis), pathologic spasm (Prinzmetal's angina), or small platelet-rich plugs also can upset the critical balance between oxygen supply and demand and thereby precipitate myocardial ischemia.

EFFECTS OF ISCHEMIA

During episodes of inadequate perfusion caused by coronary atherosclerosis, myocardial tissue oxygen tension falls and may cause transient disturbances of the mechanical, biochemical, and electrical functions of the myocardium (**Fig. 39-1**). Coronary atherosclerosis is a focal process that usually causes nonuniform ischemia. During ischemia, regional disturbances of ventricular contractility cause segmental hypokinesia, akinesia, or, in severe cases, bulging (dyskinesia), which can reduce myocardial pump function.

The abrupt development of severe ischemia, as occurs with total or subtotal coronary occlusion, is associated with almost instantaneous failure of normal muscle relaxation and then contraction. The relatively poor perfusion of the subendocardium causes more intense ischemia of this portion of the wall (compared with the subepicardial region). Ischemia of large portions of the ventricle causes transient left ventricular failure, and if the papillary muscle apparatus is involved, mitral regurgitation can occur. When ischemia is transient, it may be associated with angina pectoris; when it is prolonged, it can lead to myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction (**Chap. 41**).

A wide range of abnormalities in cell metabolism, function, and structure underlie these mechanical disturbances during ischemia. The normal myocardium metabolizes fatty acids and glucose to carbon dioxide

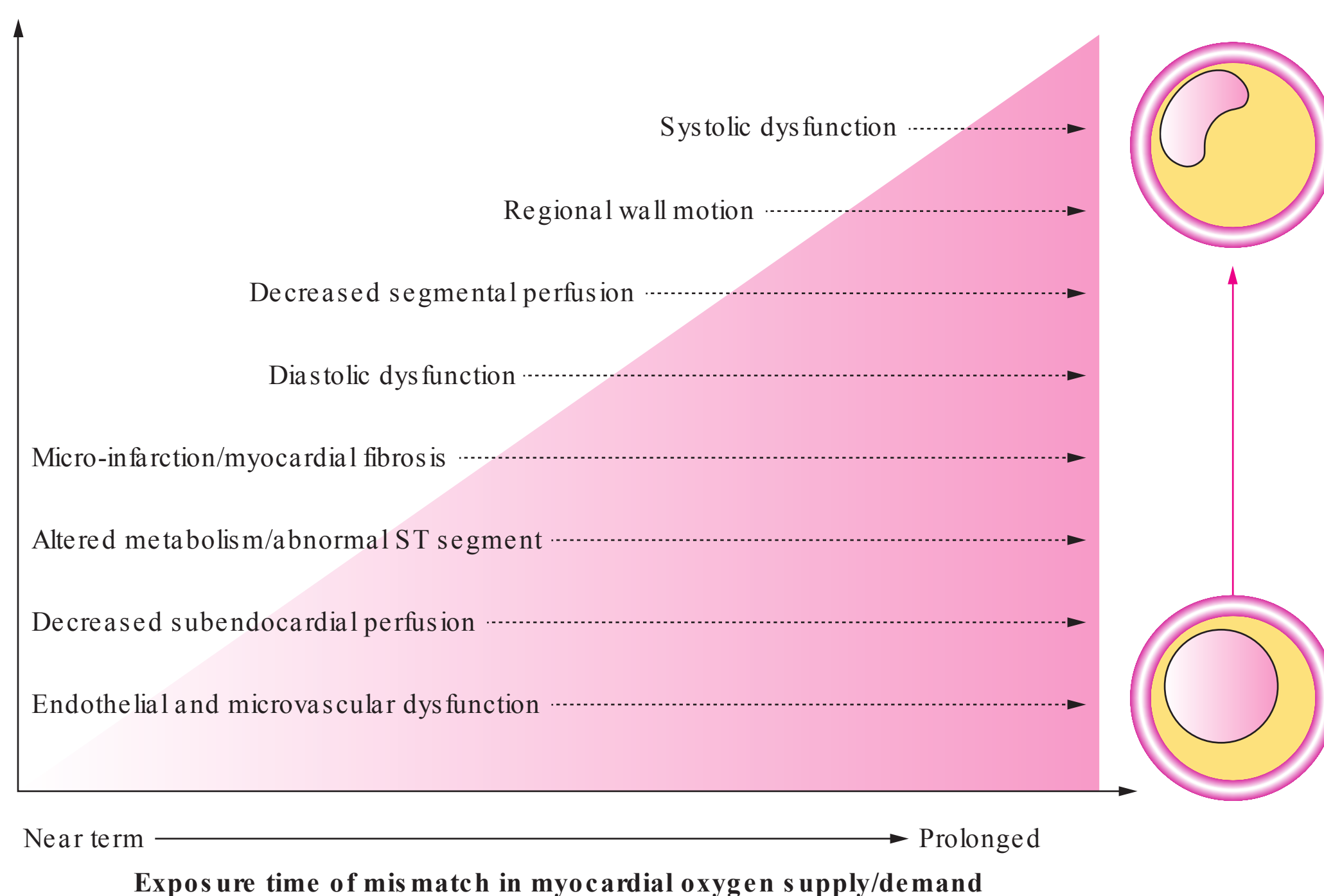


FIGURE 39-1

Cascade of mechanisms and manifestations of ischemia. (Modified from LJ Shaw et al: J Am Coll Cardiol 54:1561, 2009. Original figure illustration by Rob Flewell.)

and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is converted to lactate; intracellular pH is reduced, as are the myocardial stores of high-energy phosphates, i.e., ATP and creatine phosphate. Impaired cell membrane function leads to the leakage of potassium and the uptake of sodium by myocytes as well as an increase in cytosolic calcium. The severity and duration of the imbalance between myocardial oxygen supply and demand determine whether the damage is reversible (≤ 20 min for total occlusion in the absence of collaterals) or permanent, with subsequent myocardial necrosis (>20 min).

Ischemia also causes characteristic changes in the electrocardiogram (ECG) such as repolarization abnormalities, as evidenced by inversion of T waves and, when more severe, displacement of ST segments (**Chap. 11**). Transient T-wave inversion probably reflects nontransmural, intramyocardial ischemia; transient ST-segment depression often reflects patchy subendocardial ischemia; and ST-segment elevation is thought to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, which may lead to isolated ventricular premature beats or even ventricular tachycardia or ventricular fibrillation (**Chap. 18**). Most patients who die suddenly from IHD do so as a result of ischemia-induced ventricular tachyarrhythmias (**Chap. 35**).

ASYMPTOMATIC VERSUS SYMPTOMATIC IHD

Although the prevalence is decreasing, postmortem studies of accident victims and military casualties in Western countries still show that coronary atherosclerosis can begin before age 20 and is present even among adults who were asymptomatic during life. Exercise stress tests in asymptomatic persons may show evidence of silent myocardial ischemia, i.e., exercise-induced ECG changes not accompanied by angina pectoris; coronary angiographic studies of such persons may reveal coronary artery plaques and previously unrecognized obstructions (**Chap. 13**). Postmortem examination of patients with such obstructions without a history of clinical manifestations of myocardial ischemia often shows macroscopic scars secondary to myocardial infarction in regions supplied by diseased coronary arteries, with or without collateral circulation. According to population studies, $\approx 25\%$ of patients who survive acute myocardial infarction may not come to medical attention, and these patients have the same adverse prognosis as do those who present with the classic clinical picture of acute myocardial infarction (**Chap. 41**). Sudden death may be unheralded and is a common presenting manifestation of IHD (**Chap. 35**).

Patients with IHD also can present with cardiomegaly and heart failure secondary to ischemic damage of

the left ventricular myocardium that may have caused no symptoms before the development of heart failure; this condition is referred to as ischemic cardiomyopathy. In contrast to the asymptomatic phase of IHD, the symptomatic phase is characterized by chest discomfort due to either angina pectoris or acute myocardial infarction (**Chap. 41**). Having entered the symptomatic phase, the patient may exhibit a stable or progressive course, revert to the asymptomatic stage, or die suddenly.

STABLE ANGINA PECTORIS

The episodic clinical syndrome is due to transient myocardial ischemia. Various diseases that cause myocardial ischemia and the numerous forms of discomfort with which it may be confused are discussed in **Chap. 4**. Males constitute $\approx 70\%$ of all patients with angina pectoris and an even greater proportion of those less than 50 years of age. It is, however, important to note that angina pectoris in women is often atypical in presentation (see below).

HISTORY

The typical patient with angina is a man >50 years or a woman >60 years of age who complains of episodes of chest discomfort, usually described as heaviness, pressure, squeezing, smothering, or choking and only rarely as frank pain. When the patient is asked to localize the sensation, he or she typically places a hand over the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort (Levine's sign). Angina is usually crescendo-decrescendo in nature, typically lasts 2 to 5 min, and can radiate to either shoulder and to both arms (especially the ulnar surfaces of the forearm and hand). It also can arise in or radiate to the back, interscapular region, root of the neck, jaw, teeth, and epigastrium. Angina is rarely localized below the umbilicus or above the mandible. A useful finding in assessing a patient with chest discomfort is the fact that myocardial ischemic discomfort does not radiate to the trapezius muscles; that radiation pattern is more typical of pericarditis.

Although episodes of angina typically are caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger, fright, or frustration) and are relieved by rest, they also may occur at rest (**Chap. 40**) and while the patient is recumbent (angina decubitus). The patient may be awakened at night by typical chest discomfort and dyspnea. Nocturnal angina may be due to episodic tachycardia, diminished oxygenation as the respiratory pattern changes during sleep, or expansion of the intrathoracic blood

volume that occurs with recumbency; the latter causes an increase in cardiac size (end-diastolic volume), wall tension, and myocardial oxygen demand that can lead to ischemia and transient left ventricular failure.

The threshold for the development of angina pectoris may vary by time of day and emotional state. Many patients report a fixed threshold for angina, which occurs predictably at a certain level of activity, such as climbing two flights of stairs at a normal pace. In these patients, coronary stenosis and myocardial oxygen supply are fixed, and ischemia is precipitated by an increase in myocardial oxygen demand; they are said to have stable exertional angina. In other patients, the threshold for angina may vary considerably within any particular day and from day to day. In such patients, variations in myocardial oxygen supply, most likely due to changes in coronary vasomotor tone, may play an important role in defining the pattern of angina. A patient may report symptoms upon minor exertion in the morning (a short walk or shaving) yet by midday be capable of much greater effort without symptoms. Angina may also be precipitated by unfamiliar tasks, a heavy meal, exposure to cold, or a combination of these factors.

Exertional angina typically is relieved in 1–5 min by slowing or ceasing activities and even more rapidly by rest and sublingual nitroglycerin (see below). Indeed, the diagnosis of angina should be suspect if it does not respond to the combination of these measures. The severity of angina can be conveniently summarized

by the Canadian Cardiac Society functional classification (**Table 39-1**). Its impact on the patient's functional capacity can be described by using the New York Heart Association functional classification (Table 39-1).

Sharp, fleeting chest pain or a prolonged, dull ache localized to the left submammary area is rarely due to myocardial ischemia. However, especially in women and diabetic patients, angina pectoris may be atypical in location and not strictly related to provoking factors. In addition, this symptom may exacerbate and remit over days, weeks, or months. Its occurrence can be seasonal, occurring more frequently in the winter in temperate climates. Anginal “equivalents” are symptoms of myocardial ischemia other than angina. They include dyspnea, nausea, fatigue, and faintness and are more common in the elderly and in diabetic patients.

Systematic questioning of a patient with suspected IHD is important to uncover the features of an unstable syndrome associated with increased risk, such as angina occurring with less exertion than in the past, occurring at rest, or awakening the patient from sleep. Since coronary atherosclerosis often is accompanied by similar lesions in other arteries, a patient with angina should be questioned and examined for peripheral arterial disease (intermittent claudication [**Chap. 47**]), stroke, or transient ischemic attacks. It is also important to uncover a family history of premature IHD (<55 years in first-degree male relatives and <65 in female relatives) and the presence of diabetes mellitus, hyperlipidemia,

TABLE 39-1

CARDIOVASCULAR DISEASE CLASSIFICATION CHART		
CLASS	NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION	CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina present with strenuous or rapid or prolonged exertion at work or recreation.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions.
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort—anginal syndrome may be present at rest.

Source: Modified from L Goldman et al: Circulation 64:1227, 1981.

hypertension, cigarette smoking, and other risk factors for coronary atherosclerosis (**Chap. 36**).

The history of typical angina pectoris establishes the diagnosis of IHD until proven otherwise. The coexistence of advanced age, male sex, the postmenopausal state, and risk factors for atherosclerosis increase the likelihood of hemodynamically significant coronary disease. A particularly challenging problem is the evaluation and management of patients with persistent ischemic-type chest discomfort but no flow-limiting obstructions in their epicardial coronary arteries. This situation arises more often in women than in men. Potential etiologies include microvascular coronary disease (detectable on coronary reactivity testing in response to vasoactive agents such as intracoronary adenosine, acetylcholine, and nitroglycerin) and abnormal cardiac nociception. Treatment of microvascular coronary disease should focus on efforts to improve endothelial function, including nitrates, beta blockers, calcium antagonists, statins, and angiotensin-converting enzyme (ACE) inhibitors. Abnormal cardiac nociception is more difficult to manage and may be ameliorated in some cases by imipramine.

PHYSICAL EXAMINATION

The physical examination is often normal in patients with stable angina when they are asymptomatic. However, because of the increased likelihood of IHD in patients with diabetes and/or peripheral arterial disease, clinicians should search for evidence of atherosclerotic disease at other sites, such as an abdominal aortic aneurysm, carotid arterial bruits, and diminished arterial pulses in the lower extremities. The physical examination also should include a search for evidence of risk factors for atherosclerosis such as xanthelasmas and xanthomas (**Chap. 36**). Evidence for peripheral arterial disease should be sought by evaluating the pulse contour at multiple locations and comparing the blood pressure between the arms and between the arms and the legs (ankle-brachial index). Examination of the fundi may reveal an increased light reflex and arteriovenous nicking as evidence of hypertension. There also may be signs of anemia, thyroid disease, and nicotine stains on the fingertips from cigarette smoking.

Palpation may reveal cardiac enlargement and abnormal contraction of the cardiac impulse (left ventricular dyskinesia). Auscultation can uncover arterial bruits, a third and/or fourth heart sound, and, if acute ischemia or previous infarction has impaired papillary muscle function, an apical systolic murmur due to mitral regurgitation. These auscultatory signs are best appreciated with the patient in the left lateral decubitus position. Aortic stenosis, aortic regurgitation (**Chap. 23**), pulmonary hypertension (**Chap. 49**),

and hypertrophic cardiomyopathy (**Chap. 27**) must be excluded, since these disorders may cause angina in the absence of coronary atherosclerosis. Examination during an anginal attack is useful, since ischemia can cause transient left ventricular failure with the appearance of a third and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema. Tenderness of the chest wall, localization of the discomfort with a single fingertip on the chest, or reproduction of the pain with palpation of the chest makes it unlikely that the pain is caused by myocardial ischemia. A protuberant abdomen may indicate that the patient has the metabolic syndrome and is at increased risk for atherosclerosis.

LABORATORY EXAMINATION

Although the diagnosis of IHD can be made with a high degree of confidence from the history and physical examination, a number of simple laboratory tests can be helpful. The urine should be examined for evidence of diabetes mellitus and renal disease (including microalbuminuria) since these conditions accelerate atherosclerosis. Similarly, examination of the blood should include measurements of lipids (cholesterol—total, LDL, HDL—and triglycerides), glucose (hemoglobin A_{1C}), creatinine, hematocrit, and, if indicated based on the physical examination, thyroid function. A chest x-ray is important as it may show the consequences of IHD, i.e., cardiac enlargement, ventricular aneurysm, or signs of heart failure. These signs can support the diagnosis of IHD and are important in assessing the degree of cardiac damage. Evidence exists that an elevated level of high-sensitivity C-reactive protein (CRP) (specifically, between 0 and 3 mg/dL) is an independent risk factor for IHD and may be useful in therapeutic decision making about the initiation of hypolipidemic treatment. The major benefit of high-sensitivity CRP is in reclassifying the risk of IHD in patients in the “intermediate” risk category on the basis of traditional risk factors.

ELECTROCARDIOGRAM

A 12-lead ECG recorded at rest may be normal in patients with typical angina pectoris, but there may also be signs of an old myocardial infarction (**Chap. 11**). Although repolarization abnormalities, i.e., ST-segment and T-wave changes, as well as left ventricular hypertrophy and disturbances of cardiac rhythm or intraventricular conduction are suggestive of IHD, they are nonspecific, since they also can occur in pericardial, myocardial, and valvular heart disease or, in the case of the former, transiently with anxiety, changes in posture, drugs, or esophageal disease. The presence of left ventricular hypertrophy (LVH) is a significant indication of

increased risk of adverse outcomes from IHD. Of note, even though LVH and cardiac rhythm disturbances are nonspecific indicators of the development of IHD, they may be contributing factors to episodes of angina in patients in whom IHD has developed as a consequence of conventional risk factors. Dynamic ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific.

STRESS TESTING

Electrocardiographic

The most widely used test for both the diagnosis of IHD and the estimation of risk and prognosis involves recording the 12-lead ECG before, during, and after exercise, usually on a treadmill (Fig. 39-2). The test consists of a standardized incremental increase in external workload (Table 39-2) while symptoms, the ECG, and arm blood pressure are monitored. Exercise duration is usually symptom-limited, and the test is discontinued upon evidence of chest discomfort, severe shortness of

breath, dizziness, severe fatigue, ST-segment depression >0.2 mV (2 mm), a fall in systolic blood pressure >10 mmHg, or the development of a ventricular tachyarrhythmia. The test is used to discover any limitation in exercise performance, detect typical ECG signs of myocardial ischemia, and establish their relationship to chest discomfort. The ischemic ST-segment response generally is defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 s (Fig. 39-1). Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Although T-wave abnormalities, conduction disturbances, and ventricular arrhythmias that develop during exercise should be noted, they are also not diagnostic. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered nondiagnostic.

In interpreting ECG stress tests, the probability that coronary artery disease (CAD) exists in the patient or population under study (i.e., pretest probability) should

TABLE 39-2

RELATION OF METABOLIC EQUIVALENT TASKS (METs) TO STAGES IN VARIOUS TESTING PROTOCOLS

FUNCTIONAL CLASS	CLINICAL STATUS	O ₂ COST ML/KG/MIN	METS	TREADMILL PROTOCOLS			
				BRUCE Modified 3 min Stages		BRUCE 3 min Stages	
				MPH	%GR	MPH	%GR
NORMAL AND I				6.0	22	6.0	22
	HEALTHY,			5.5	20	5.2	20
	DEPENDENT			5.0	18	5.0	18
	ON AGE,	56.0	16				
	ACTIVITY	52.5	15				
		49.0	14				
		45.5	13	4.2	16	4.2	16
		42.0	12				
		38.5	11	3.4	14	3.4	14
	SEDENTARY	35.0	10				
II	HEALTHY	31.5	9				
		28.0	8				
	LIMITED	24.5	7	2.5	12	2.5	12
III	SYMPTOMATIC	21.0	6				
		17.5	5	1.7	10	1.7	10
IV		14.0	4				
		10.5	3	1.7	5		
		7.0	2	1.7	0		
		3.5	1				

Abbreviations: GR, grade; MPH, miles per hour.

Source: Modified from GF Fletcher et al: Circulation 104:1694, 2001.

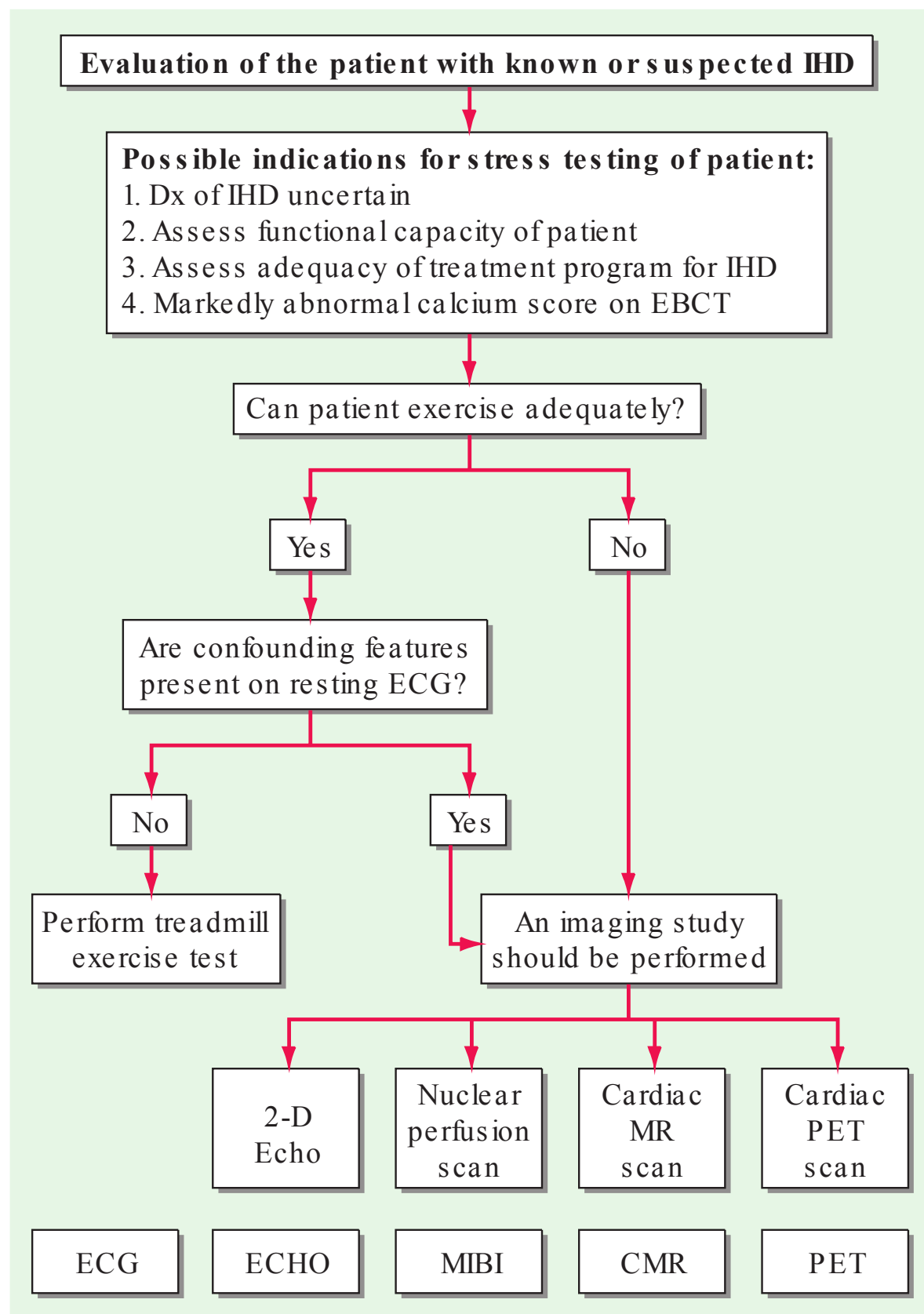


FIGURE 39-2

Evaluation of the patient with known or suspected ischemic heart disease. On the left of the figure is an algorithm for identifying patients who should be referred for stress testing and the decision pathway for determining whether a standard treadmill exercise with electrocardiogram (ECG) monitoring alone is adequate. A specialized imaging study is necessary if the patient cannot exercise adequately (pharmacologic challenge is given) or if there are confounding features on the resting ECG (symptom-limited treadmill exercise may be used to stress the coronary circulation). Panels B–E, continued on the next page, are examples of the data obtained with ECG monitoring and specialized imaging procedures. CMR, cardiac magnetic resonance; EBCT, electron beam computed tomography; ECHO, echocardiography; IHD, ischemic heart disease; MIBI, methoxyisobutyl isonitrite; MR, magnetic resonance; PET, positron emission tomography.

A. Lead V₄ at rest (top panel) and after 4.5 min of exercise (bottom panel). There is 3 mm (0.3 mV) of horizontal ST-segment depression, indicating a positive test for ischemia. (Modified from BR Chaitman, in E Braunwald et al [eds]: Heart Disease, 8th ed, Philadelphia, Saunders, 2008.)

B. A 45-year-old avid jogger who began experiencing classic substernal chest pressure underwent an exercise echo study. With exercise the patient's heart rate increased from 52 to 153 beats/min. The left ventricular chamber dilated with exercise, and the septal and apical portions became akinetic to dyskinetic (red arrow). These findings are strongly suggestive of a significant flow-limiting stenosis in the proximal left anterior descending artery, which was confirmed at coronary angiography. (Modified from SD Solomon, in E Braunwald et al [eds]: Primary Cardiology, 2nd ed, Philadelphia, Saunders, 2003.)

C. Stress and rest myocardial perfusion single-photon emission computed tomography images obtained with 99m-technetium sestamibi



A

in a patient with chest pain and dyspnea on exertion. The images demonstrate a medium-size and severe stress perfusion defect involving the inferolateral and basal inferior walls, showing nearly complete reversibility, consistent with moderate ischemia in the right coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.)

D. A patient with a prior myocardial infarction presented with recurrent chest discomfort. On cardiac magnetic resonance (CMR) cine imaging, a large area of anterior akinesia was noted (marked by the arrows in the top left and right images, systolic frame only). This area of akinesia was matched by a larger extent of late gadolinium-DTPA enhancements consistent with a large transmural myocardial infarction (marked by arrows in the middle left and right images). Resting (bottom left) and adenosine vasodilating stress (bottom right) first-pass perfusion images revealed reversible perfusion abnormality that extended to the inferior septum. This patient was found to have an occluded proximal left anterior descending coronary artery with extensive collateral formation. This case illustrates the utility of different modalities in a CMR examination in characterizing ischemic and infarcted myocardium. DTPA, diethylenetriamine penta-acetic acid. (Images provided by Dr. Raymond Kwong, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.)

E. Stress and rest myocardial perfusion PET images obtained with rubidium-82 in a patient with chest pain on exertion. The images demonstrate a large and severe stress perfusion defect involving the mid and apical anterior, anterolateral, and anteroapical walls and the left ventricular apex, showing complete reversibility, consistent with extensive and severe ischemia in the mid-left anterior descending coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.)

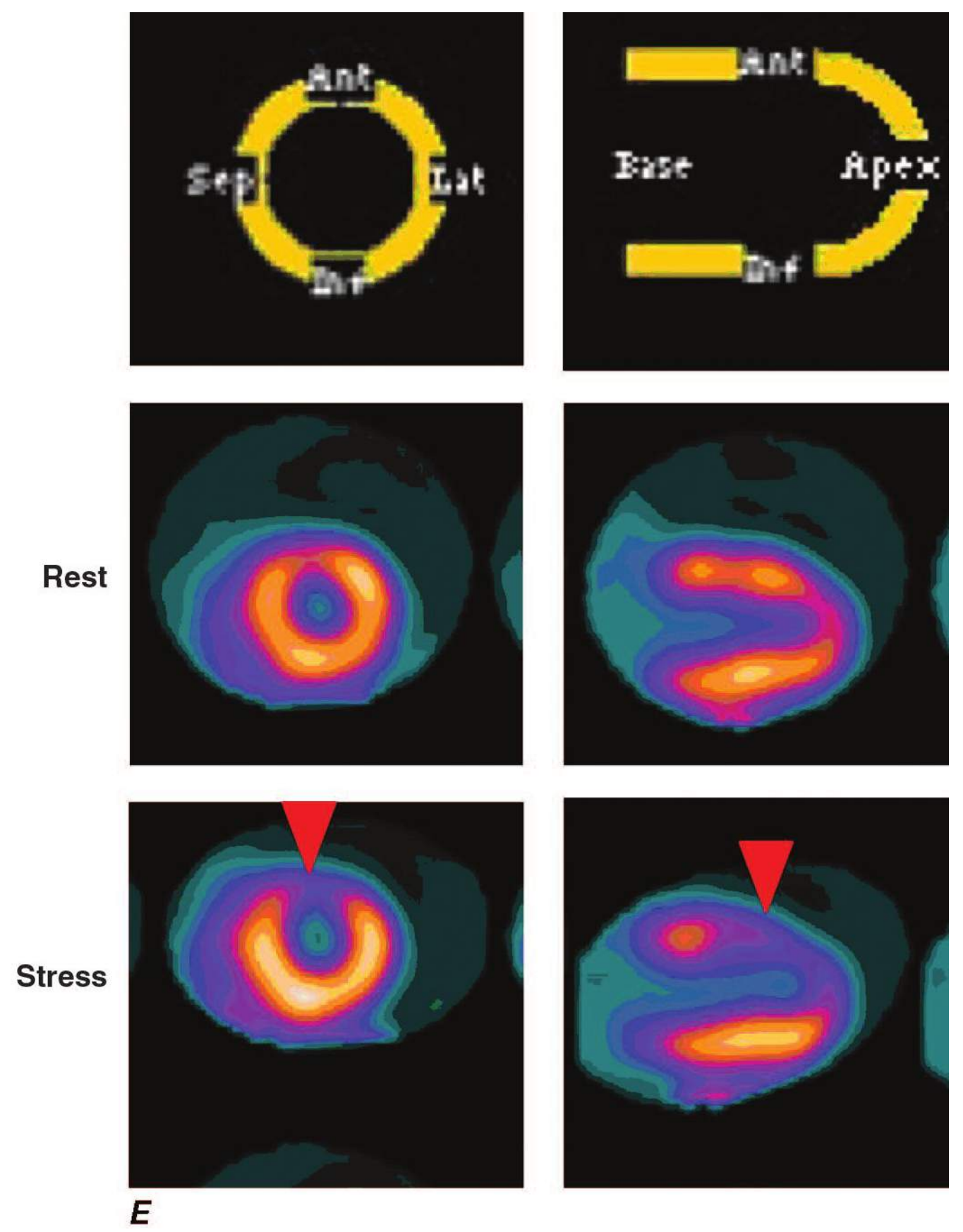
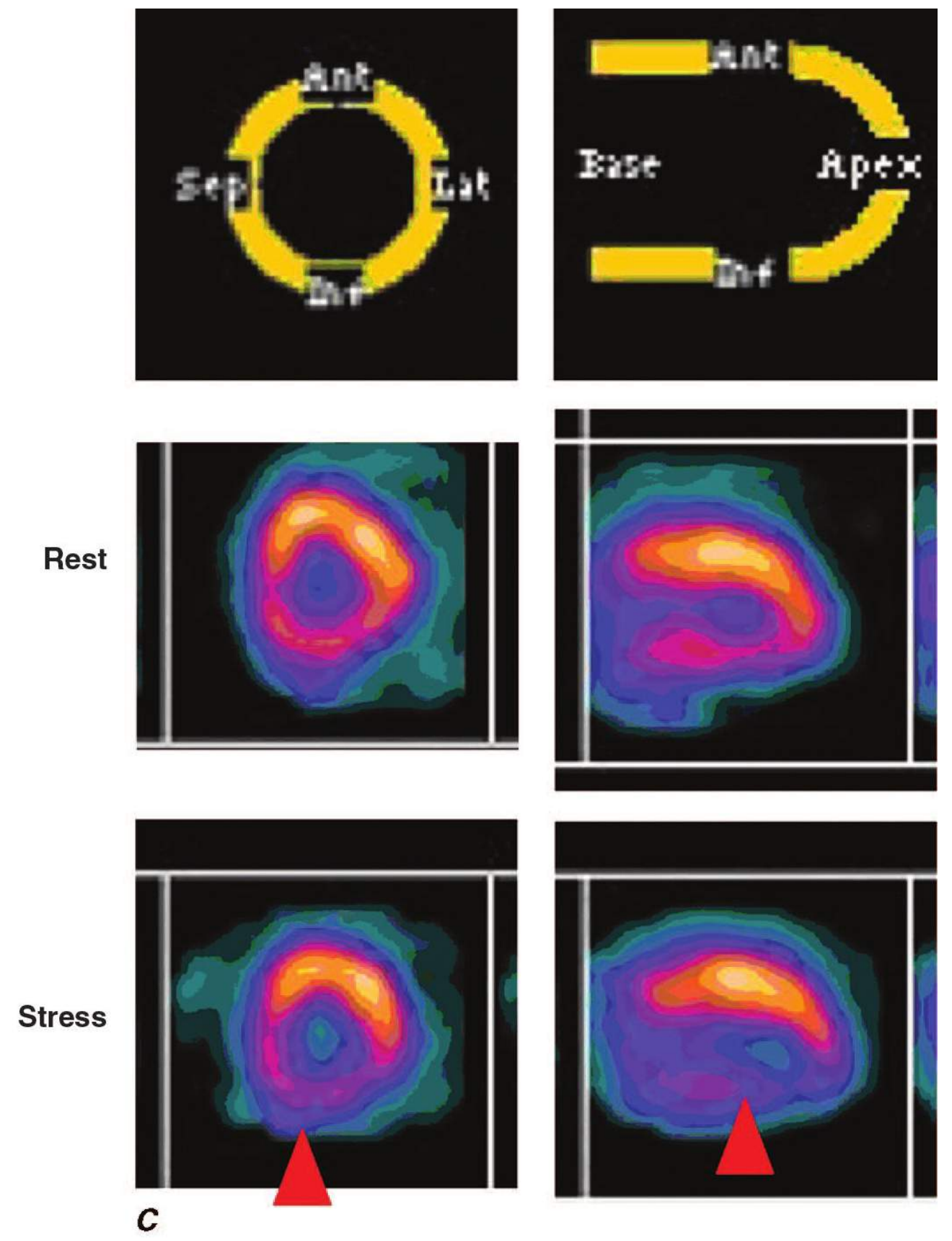
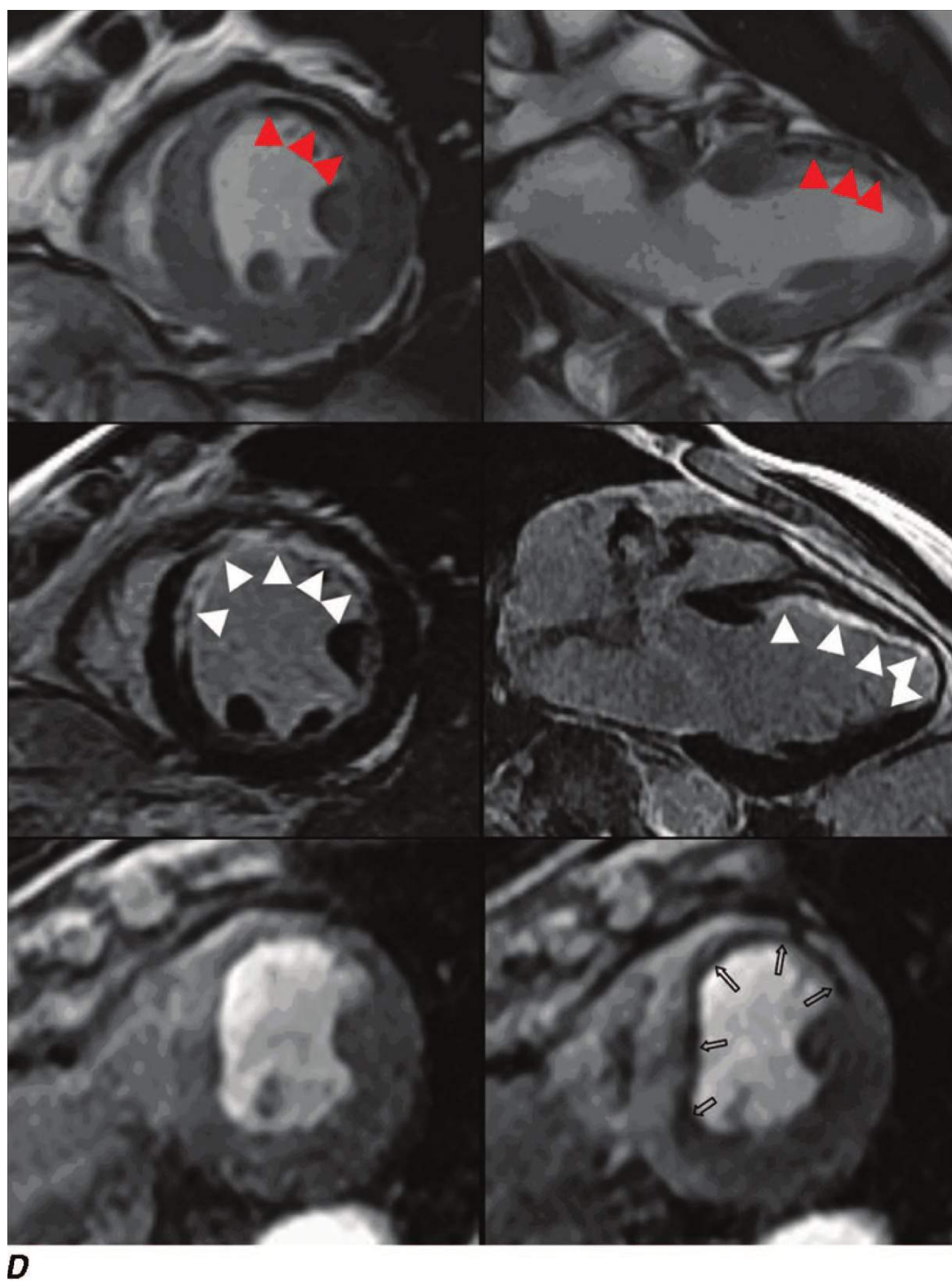
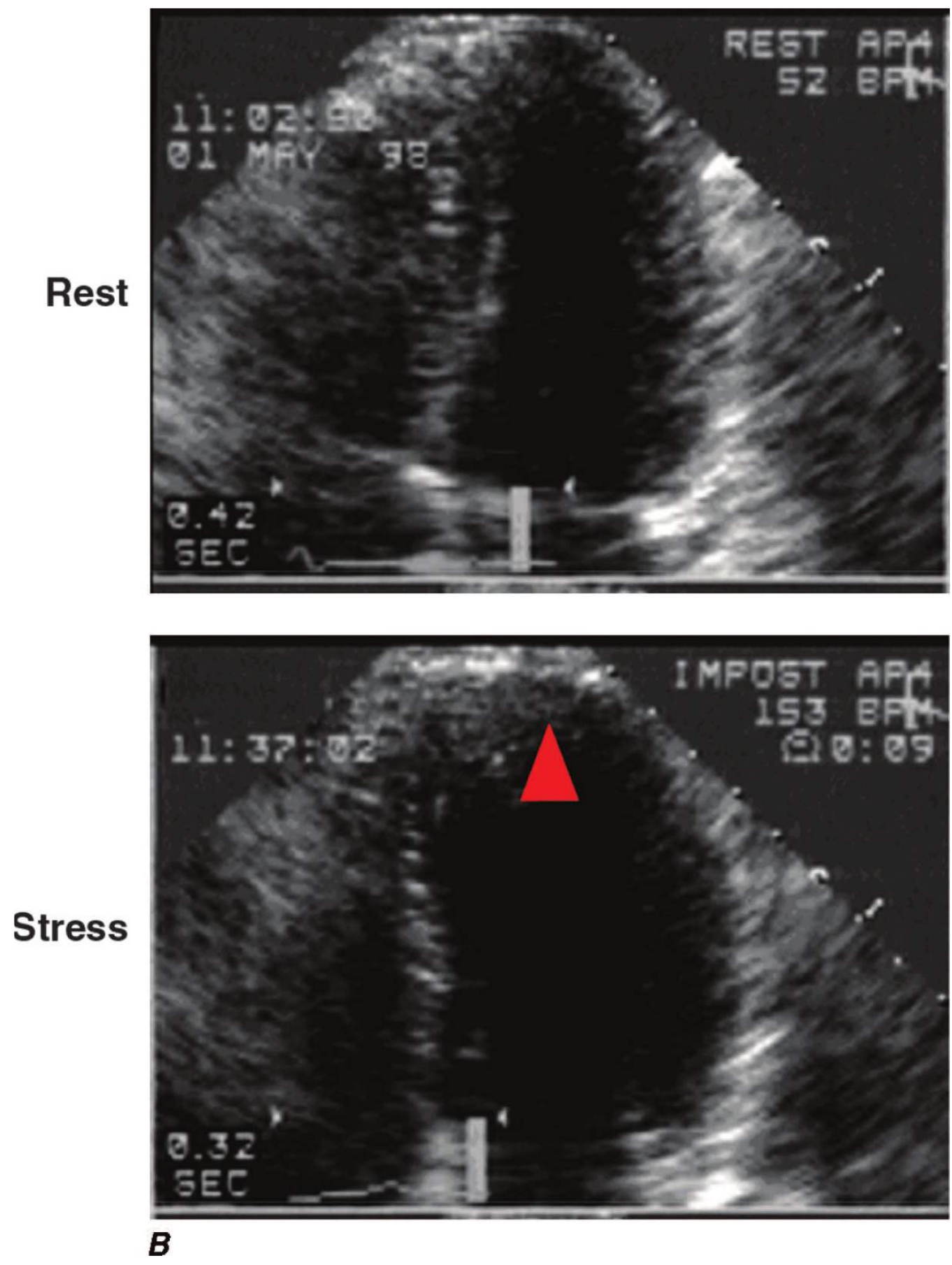


FIGURE 39-2 (continued)

be considered. Overall, false-positive or false-negative results occur in one-third of cases. However, a positive result on exercise indicates that the likelihood of CAD is 98% in males who are >50 years with a history of typical angina pectoris and who develop chest discomfort during the test. The likelihood decreases if the patient has atypical or no chest pain by history and/or during the test.

The incidence of false-positive tests is significantly increased in patients with low probabilities of IHD, such as asymptomatic men age <40 or premenopausal women with no risk factors for premature atherosclerosis. It is also increased in patients taking cardioactive drugs, such as digitalis and antiarrhythmic agents, and in those with intraventricular conduction disturbances, resting ST-segment and T-wave abnormalities, ventricular hypertrophy, or abnormal serum potassium levels. Obstructive disease limited to the circumflex coronary artery may result in a false-negative stress test since the lateral portion of the heart that this vessel supplies is not well represented on the surface 12-lead ECG. Since the overall sensitivity of exercise stress electrocardiography is only $\approx 75\%$, a negative result does not exclude CAD, although it makes the likelihood of three-vessel or left main CAD extremely unlikely.

A medical professional should be present throughout the exercise test. It is important to measure total duration of exercise, the times to the onset of ischemic ST-segment change and chest discomfort, the external work performed (generally expressed as the stage of exercise), and the internal cardiac work performed, i.e., by the heart rate–blood pressure product. The depth of the ST-segment depression and the time needed for recovery of these ECG changes are also important. Because the risks of exercise testing are small but real—estimated at one fatality and two nonfatal complications per 10,000 tests—equipment for resuscitation should be available. Modified (heart rate–limited rather than symptom–limited) exercise tests can be performed safely in patients as early as 6 days after uncomplicated myocardial infarction (Table 39-2). Contraindications to exercise stress testing include rest angina within 48 h, unstable rhythm, severe aortic stenosis, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

The normal response to graded exercise includes progressive increases in heart rate and blood pressure. Failure of the blood pressure to increase or an actual decrease with signs of ischemia during the test is an important adverse prognostic sign, since it may reflect ischemia-induced global left ventricular dysfunction. The development of angina and/or severe (>0.2 mV) ST-segment depression at a low workload, i.e., before completion of stage II of the Bruce protocol, and/or ST-segment depression that persists >5 min after the

termination of exercise increases the specificity of the test and suggests severe IHD and a high risk of future adverse events.

Cardiac imaging

(See also Chap. 12) When the resting ECG is abnormal (e.g., preexcitation syndrome, >1 mm of resting ST-segment depression, left bundle branch block, paced ventricular rhythm), information gained from an exercise test can be enhanced by stress myocardial radionuclide perfusion imaging after the intravenous administration of thallium-201 or 99m-technetium sestamibi during exercise (or with pharmacologic) stress. Contemporary data also suggest positron emission tomography (PET) imaging (with exercise or pharmacologic stress) using N-13 ammonia or rubidium-82 nuclide as another technique for assessing perfusion. Images obtained immediately after cessation of exercise to detect regional ischemia are compared with those obtained at rest to confirm reversible ischemia and regions of persistently absent uptake that signify infarction.

A sizable fraction of patients who need noninvasive stress testing to identify myocardial ischemia and increased risk of coronary events cannot exercise because of peripheral vascular or musculoskeletal disease, exertional dyspnea, or deconditioning. In these circumstances, an intravenous pharmacologic challenge is used in place of exercise. For example, dipyridamole or adenosine can be given to create a coronary “steal” by temporarily increasing flow in nondiseased segments of the coronary vasculature at the expense of diseased segments. Alternatively, a graded incremental infusion of dobutamine may be administered to increase MVO_2 . A variety of imaging options are available to accompany these pharmacologic stressors (Fig. 39-2). The development of a transient perfusion defect with a tracer such as thallium-201 or 99m-technetium sestamibi is used to detect myocardial ischemia.

Echocardiography is used to assess left ventricular function in patients with chronic stable angina and patients with a history of a prior myocardial infarction, pathologic Q waves, or clinical evidence of heart failure. Two-dimensional echocardiography can assess both global and regional wall motion abnormalities of the left ventricle that are transient when due to ischemia. Stress (exercise or dobutamine) echocardiography may cause the emergence of regions of akinesis or dyskinesis that are not present at rest. Stress echocardiography, like stress myocardial perfusion imaging, is more sensitive than exercise electrocardiography in the diagnosis of IHD. Cardiac magnetic resonance (CMR) stress testing is also evolving as an alternative to radionuclide, PET, or echocardiographic stress imaging. CMR stress testing performed with dobutamine infusion can be

used to assess wall motion abnormalities accompanying ischemia, as well as myocardial perfusion. CMR can be used to provide more complete ventricular evaluation using multislice magnetic resonance imaging (MRI) studies.

Atherosclerotic plaques become progressively calcified over time, and coronary calcification in general increases with age. For this reason, methods for detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis. These methods involve computed tomography (CT) applications that achieve rapid acquisition of images (electron beam [EBCT] and multidetector [MDCT] detection). Coronary calcium detected by these imaging techniques most commonly is quantified by using the Agatston score, which is based on the area and density of calcification. Although the diagnostic accuracy of this imaging method is high (sensitivity, 90–94%; specificity, 95–97%; negative predictive value, 93–99%), its prognostic utility has not been defined. Thus, its role in CT, EBCT, and MDCT scans for the detection and management of patients with IHD has not been clarified.

CORONARY ARTERIOGRAPHY

(See also Chap. 13) This diagnostic method outlines the lumina of the coronary arteries and can be used to detect or exclude serious coronary obstruction. However, coronary arteriography provides no information about the arterial wall, and severe atherosclerosis that does not encroach on the lumen may go undetected. Of note, atherosclerotic plaques characteristically are scattered throughout the coronary tree, tend to occur more frequently at branch points, and grow progressively in the intima and media of an epicardial coronary artery at first without encroaching on the lumen, causing an outward bulging of the artery—a process referred to as remodeling (Chap. 36). Later in the course of the disease, further growth causes luminal narrowing.

Indications

Coronary arteriography is indicated in (1) patients with chronic stable angina pectoris who are severely symptomatic despite medical therapy and are being considered for revascularization, i.e., a percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); (2) patients with troublesome symptoms that present diagnostic difficulties in whom there is a need to confirm or rule out the diagnosis of IHD; (3) patients with known or possible angina pectoris who have survived cardiac arrest; (4) patients with angina or evidence of ischemia on noninvasive testing with clinical or laboratory evidence of ventricular dysfunction; and

(5) patients judged to be at high risk of sustaining coronary events based on signs of severe ischemia on noninvasive testing, regardless of the presence or severity of symptoms (see below).

Examples of other indications for coronary arteriography include the following:

1. Patients with chest discomfort suggestive of angina pectoris but a negative or nondiagnostic stress test who require a definitive diagnosis for guiding medical management, alleviating psychological stress, career or family planning, or insurance purposes.
2. Patients who have been admitted repeatedly to the hospital for a suspected acute coronary syndrome (**Chaps. 40 and 41**), but in whom this diagnosis has not been established and in whom the presence or absence of CAD should be determined.
3. Patients with careers that involve the safety of others (e.g., pilots, firefighters, police) who have questionable symptoms or suspicious or positive noninvasive tests and in whom there are reasonable doubts about the state of the coronary arteries.
4. Patients with aortic stenosis or hypertrophic cardiomyopathy and angina in whom the chest pain could be due to IHD.
5. Male patients >45 years and females >55 years who are to undergo a cardiac operation such as valve replacement or repair and who may or may not have clinical evidence of myocardial ischemia.
6. Patients after myocardial infarction, especially those who are at high risk after myocardial infarction because of the recurrence of angina or the presence of heart failure, frequent ventricular premature contractions, or signs of ischemia on the stress test.
7. Patients with angina pectoris, regardless of severity, in whom noninvasive testing indicates a high risk of coronary events (poor exercise performance or severe ischemia).
8. Patients in whom coronary spasm or another non-atherosclerotic cause of myocardial ischemia (e.g., coronary artery anomaly, Kawasaki disease) is suspected.

Noninvasive alternatives to diagnostic coronary arteriography include CT angiography and CMR angiography (**Chap. 12**). Although these new imaging techniques can provide information about obstructive lesions in the epicardial coronary arteries, their exact role in clinical practice has not been rigorously defined. Important aspects of their use that should be noted include the substantially higher radiation exposure with CT angiography compared to conventional diagnostic arteriography and the limitations on CMR imposed by cardiac movement during the cardiac cycle, especially at high heart rates.

PROGNOSIS

The principal prognostic indicators in patients known to have IHD are age, the functional state of the left ventricle, the location(s) and severity of coronary artery narrowing, and the severity or activity of myocardial ischemia. Angina pectoris of recent onset, unstable angina (**Chap. 40**), early postmyocardial infarction angina, angina that is unresponsive or poorly responsive to medical therapy, and angina accompanied by symptoms of congestive heart failure all indicate an increased risk for adverse coronary events. The same is true for the physical signs of heart failure, episodes of pulmonary edema, transient third heart sounds, and mitral regurgitation and for echocardiographic or radioisotopic (or roentgenographic) evidence of cardiac enlargement and reduced (<0.40) ejection fraction.

Most important, any of the following signs during noninvasive testing indicates a high risk for coronary events: inability to exercise for 6 min, i.e., stage II (Bruce protocol) of the exercise test; a strongly positive exercise test showing onset of myocardial ischemia at low workloads (≥ 0.1 mV ST-segment depression before completion of stage II, ≥ 0.2 mV ST-segment depression at any stage, ST-segment depression for >5 min after the cessation of exercise, a decline in systolic pressure >10 mmHg during exercise, or the development of ventricular tachyarrhythmias during exercise); the development of large or multiple perfusion defects or increased lung uptake during stress radioisotope perfusion imaging; and a decrease in left ventricular ejection fraction during exercise on radionuclide ventriculography or during stress echocardiography. Conversely, patients who can complete stage III of the Bruce exercise protocol and have a normal stress perfusion scan or negative stress echocardiographic evaluation are at very low risk for future coronary events. The finding of frequent episodes of ST-segment deviation on ambulatory ECG monitoring (even in the absence of symptoms) is also an adverse prognostic finding.

On cardiac catheterization, elevations of left ventricular end-diastolic pressure and ventricular volume and reduced ejection fraction are the most important signs of left ventricular dysfunction and are associated with a poor prognosis. Patients with chest discomfort but normal left ventricular function and normal coronary arteries have an excellent prognosis. Obstructive lesions of the left main ($>50\%$ luminal diameter) or left anterior descending coronary artery proximal to the origin of the first septal artery are associated with a greater risk than are lesions of the right or left circumflex coronary artery because of the greater quantity of myocardium at risk. Atherosclerotic plaques in epicardial arteries with fissuring or filling defects indicate increased risk. These lesions go through phases of inflammatory cellular activity, degeneration, endothelial

dysfunction, abnormal vasomotion, platelet aggregation, and fissuring or hemorrhage. These factors can temporarily worsen the stenosis and cause thrombosis and/or abnormal reactivity of the vessel wall, thus exacerbating the manifestations of ischemia. The recent onset of symptoms, the development of severe ischemia during stress testing (see above), and unstable angina pectoris (**Chap. 40**) all reflect episodes of rapid progression in coronary lesions.

With any degree of obstructive CAD, mortality is greatly increased when left ventricular function is impaired; conversely, at any level of left ventricular function, the prognosis is influenced importantly by the quantity of myocardium perfused by critically obstructed vessels. Therefore, it is essential to collect all the evidence substantiating past myocardial damage (evidence of myocardial infarction on ECG, echocardiography, radioisotope imaging, or left ventriculography), residual left ventricular function (ejection fraction and wall motion), and risk of future damage from coronary events (extent of coronary disease and severity of ischemia defined by noninvasive stress testing). The larger the quantity of established myocardial necrosis is, the less the heart is able to withstand additional damage and the poorer the prognosis is. Risk estimation must include age, presenting symptoms, all risk factors, signs of arterial disease, existing cardiac damage, and signs of impending damage (i.e., ischemia).

The greater the number and severity of risk factors for coronary atherosclerosis (advanced age [>75 years], hypertension, dyslipidemia, diabetes, morbid obesity, accompanying peripheral and/or cerebrovascular disease, previous myocardial infarction), the worse the prognosis of an angina patient. Evidence exists that elevated levels of CRP in the plasma, extensive coronary calcification on electron beam CT (see above), and increased carotid intimal thickening on ultrasound examination also indicate an increased risk of coronary events.

TREATMENT Stable Angina Pectoris

Once the diagnosis of IHD has been made, each patient must be evaluated individually with respect to his or her level of understanding, expectations and goals, control of symptoms, and prevention of adverse clinical outcomes such as myocardial infarction and premature death. The degree of disability and the physical and emotional stress that precipitates angina must be recorded carefully to set treatment goals. The management plan should include the following components: (1) explanation of the problem and reassurance about the ability to formulate a treatment plan, (2) identification and treatment of aggravating conditions, (3) recommendations for adaptation of activity as needed, (4) treatment of risk factors that will decrease the occurrence of adverse coronary

outcomes, (5) drug therapy for angina, and (6) consideration of revascularization.

EXPLANATION AND REASSURANCE Patients with IHD need to understand their condition and realize that a long and productive life is possible even though they have angina pectoris or have experienced and recovered from an acute myocardial infarction. Offering results of clinical trials showing improved outcomes can be of great value in encouraging patients to resume or maintain activity and return to work. A planned program of rehabilitation can encourage patients to lose weight, improve exercise tolerance, and control risk factors with more confidence.

IDENTIFICATION AND TREATMENT OF AGGRAVATING CONDITIONS A number of conditions may increase oxygen demand or decrease oxygen supply to the myocardium and may precipitate or exacerbate angina in patients with IHD. Left ventricular hypertrophy, aortic valve disease, and hypertrophic cardiomyopathy may cause or contribute to angina and should be excluded or treated. Obesity, hypertension, and hyperthyroidism should be treated aggressively to reduce the frequency and severity of anginal episodes. Decreased myocardial oxygen supply may be due to reduced oxygenation of the arterial blood (e.g., in pulmonary disease or, when carboxyhemoglobin is present, due to cigarette or cigar smoking) or decreased oxygen-carrying capacity (e.g., in anemia). Correction of these abnormalities, if present, may reduce or even eliminate angina pectoris.

ADAPTATION OF ACTIVITY Myocardial ischemia is caused by a discrepancy between the demand of the heart muscle for oxygen and the ability of the coronary circulation to meet that demand. Most patients can be helped to understand this concept and utilize it in the rational programming of activity. Many tasks that ordinarily evoke angina may be accomplished without symptoms simply by reducing the speed at which they are performed. Patients must appreciate the diurnal variation in their tolerance of certain activities and should reduce their energy requirements in the morning, immediately after meals, and in cold or inclement weather. On occasion, it may be necessary to recommend a change in employment or residence to avoid physical stress.

Physical conditioning usually improves the exercise tolerance of patients with angina and has substantial psychological benefits. A regular program of isotonic exercise that is within the limits of the individual patient's threshold for the development of angina pectoris and that does not exceed 80% of the heart rate associated with ischemia on exercise testing should be strongly encouraged. Based on the results of an exercise test, the number of metabolic equivalent tasks (METs) performed at the onset of ischemia can be estimated (Table 39-2) and a practical exercise prescription can be formulated to permit daily activities that will fall below the ischemic threshold (Table 39-3).

TREATMENT OF RISK FACTORS A family history of premature IHD is an important indicator of increased risk and should trigger a search for treatable risk factors such as hyperlipidemia, hyper-

tension, and diabetes mellitus. Obesity impairs the treatment of other risk factors and increases the risk of adverse coronary events. In addition, obesity often is accompanied by three other risk factors: diabetes mellitus, hypertension, and hyperlipidemia. The treatment of obesity and these accompanying risk factors is an important component of any management plan. A diet low in saturated and trans-unsaturated fatty acids and a reduced caloric intake to achieve optimal body weight are a cornerstone in the management of chronic IHD. It is especially important to emphasize weight loss and regular exercise in patients with the metabolic syndrome or overt diabetes mellitus.

Cigarette smoking accelerates coronary atherosclerosis in both sexes and at all ages and increases the risk of thrombosis, plaque instability, myocardial infarction, and death (**Chap. 36**). In addition, by increasing myocardial oxygen needs and reducing oxygen supply, it aggravates angina. Smoking cessation studies have demonstrated important benefits with a significant decline in the occurrence of these adverse outcomes. The physician's message must be clear and strong and supported by programs that achieve and monitor abstinence. Hypertension (**Chap. 43**) is associated with an increased risk of adverse clinical events from coronary atherosclerosis as well as stroke. In addition, the left ventricular hypertrophy that results from sustained hypertension aggravates ischemia. There is evidence that long-term effective treatment of hypertension can decrease the occurrence of adverse coronary events.

Diabetes mellitus accelerates coronary and peripheral atherosclerosis and is frequently associated with dyslipidemias and increases in the risk of angina, myocardial infarction, and sudden coronary death. Aggressive control of the dyslipidemia (target LDL cholesterol <70 mg/dL) and hypertension (target blood pressure 120/80 mmHg) that are frequently found in diabetic patients is highly effective and therefore essential, as described below.

DYSLIPIDEMIA The treatment of dyslipidemia is central in aiming for long-term relief from angina, reduced need for revascularization, and reduction in myocardial infarction and death. The control of lipids can be achieved by the combination of a diet low in saturated and trans-unsaturated fatty acids, exercise, and weight loss. Nearly always, HMG-CoA reductase inhibitors (statins) are required and can lower LDL cholesterol (25–50%), raise HDL cholesterol (5–9%), and lower triglycerides (5–30%). A powerful treatment effect of statins on atherosclerosis, IHD, and outcomes is seen regardless of the pretreatment LDL cholesterol level. Fibrates or niacin can be used to raise HDL cholesterol and lower triglycerides (**Chaps. 36 and 37**). Controlled trials with lipid-regulating regimens have shown equal proportional benefit for men, women, the elderly, diabetic patients, and smokers.

Compliance with the health-promoting behaviors listed above is generally very poor, and a conscientious physician must not underestimate the major effort required to meet this challenge. Many patients who are discharged from the hospital with proven coronary disease do not receive adequate treatment

TABLE 39-3

ENERGY REQUIREMENTS FOR SOME COMMON ACTIVITIES				
LESS THAN 3 METs	3–5 METs	5–7 METs	7–9 METs	MORE THAN 9 METs
Self-Care				
Washing/shaving Dressing	Cleaning windows Raking	Easy digging in garden Level hand lawn mowing	Heavy shoveling Carrying objects (60–90 lb)	Carrying loads up stairs (objects more than 90 lb) Climbing stairs (quickly)
Light housekeeping	Power lawn mowing	Carrying objects (30–60 lb)		Shoveling heavy snow
Desk work	Bed making/stripping			
Driving auto	Carrying objects (15–30 lb)			
Occupational				
Sitting (clerical/assembly) Desk work	Stocking shelves (light objects) Light welding/carpentry	Carpentry (exterior) Shoveling dirt	Digging ditches (pick and shovel)	Heavy labor
Standing (store clerk)		Sawing wood		
Recreational				
Golf (cart)	Dancing (social)	Tennis (singles)	Canoeing	Squash
Knitting	Golf (walking)	Snow skiing (downhill)	Mountain climbing	Ski touring
	Sailing	Light backpacking		Vigorous basketball
	Tennis (doubles)	Basketball		
		Stream fishing		
Physical Conditioning				
Walking (2 mph)	Level walking (3–4 mph)	Level walking (4.5–5.0 mph)	Level jogging (5 mph)	Running more than 6 mph
Stationary bike	Level biking (6–8 mph)	Bicycling (9–10 mph)	Swimming (crawl stroke)	Bicycling (more than 13 mph)
Very light calisthenics	Light calisthenics	Swimming, breast stroke	Rowing machine Heavy calisthenics Bicycling (12 mph)	Rope jumping Walking uphill (5 mph)

Abbreviation: METs, metabolic equivalent tasks.
Source: Modified from WL Haskell: Rehabilitation of the coronary patient, in NK Wenger, HK Hellerstein (eds): Design and Implementation of Cardiac Conditioning Program. New York, Churchill Livingstone, 1978.

for dyslipidemia. In light of the proof that treating dyslipidemia brings major benefits, physicians need to establish treatment pathways, monitor compliance, and follow up regularly.

RISKREDUCTIONINWOMENWITHIHD The incidence of clinical IHD in premenopausal women is very low; however, after menopause, the atherogenic risk factors increase (e.g., increased LDL, reduced HDL) and the rate of clinical coronary events accelerates to the levels observed in men. Women have not given up cigarette smoking as effectively as have men. Diabetes mellitus, which is more common in women, greatly increases the occurrence of clinical IHD and amplifies the deleterious effects of hypertension, hyperlipidemia, and smoking. Cardiac catheterization and coronary revascularization are underused in women and are performed at a later and more severe stage of the disease than in men. When cholesterol lowering, beta blockers after myocardial infarction, and coronary artery bypass grafting are applied in the appropriate patient groups, women benefit to the same degree as men.

DRUGTHERAPY The commonly used drugs for the treatment of angina pectoris are summarized in **Tables 39-4 through 39-6**. Pharmacotherapy for IHD is designed to reduce the frequency of anginal episodes, myocardial infarction, and coronary death. There is a wealth of trial data to emphasize how important this medical management is when added to the health-promoting behaviors discussed above. To achieve maximum benefit from medical therapy for IHD, it is frequently necessary to combine agents from different classes and titrate the doses as guided by the individual profile of risk factors, symptoms, hemodynamic responses, and side effects.

NITRATES The organic nitrates are a valuable class of drugs in the management of angina pectoris (Table 39-4). Their major mechanisms of action include systemic venodilation with concomitant reduction in left ventricular end-diastolic volume and pressure, thereby reducing myocardial wall tension and oxygen requirements; dilation of epicardial coronary vessels; and increased blood flow in collateral vessels. When

TABLE 39-4

NITRATE THERAPY IN PATIENTS WITH ISCHEMIC HEART DISEASE

PREPARATION OF AGENT	DOSE	SCHEDULE
Nitroglycerin ^a		
Ointment	0.5–2 inches	Two or three times daily
Transdermal patch	0.2–0.8 mg/h	Every 24 h; remove at bedtime for 12–14 h
Sublingual tablet	0.3–0.6 mg	As needed, up to three doses 5 min apart
Spray	One or two sprays	As needed, up to three doses 5 min apart
Isosorbide dinitrate ^a		
Oral	10–40 mg	Two or three times daily
Oral sustained release	80–120 mg	Once or twice daily (eccentric schedules)
Isosorbide 5-mononitrate		
Oral	20 mg	Twice daily (given 7–8 h apart)
Oral sustained release	30–240 mg	Once daily

^aA 10- to 12-h nitrate-free interval is recommended.

Source: Modified from DA Morrow, WE Boden: Stable ischemic heart disease. In RO Bonow et al (eds): Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th edition. Philadelphia, Saunders, 2012, p. 1224.

metabolized, organic nitrates release nitric oxide (NO) that binds to guanylyl cyclase in vascular smooth muscle cells, leading to an increase in cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle. Nitrates also exert antithrombotic activity by NO-dependent activation of platelet guanylyl cyclase, impairment of intraplatelet calcium flux, and platelet activation.

The absorption of these agents is most rapid and complete through the mucous membranes. For this reason, nitroglycerin is most commonly administered sublingually in tablets of 0.4 or 0.6 mg. Patients with angina should be instructed to take the medication both to relieve angina and also approximately 5 min before stress that is likely to induce an episode. The value of this prophylactic use of the drug cannot be overemphasized.

Nitrates improve exercise tolerance in patients with chronic angina and relieve ischemia in patients with unstable angina as well as patients with Prinzmetal's variant angina (**Chap. 40**). A diary of angina and nitroglycerin use may be valuable for detecting changes in the frequency, severity, or threshold for discomfort that may signify the development of unstable angina pectoris and/or herald an impending myocardial infarction.

Long-acting Nitrates None of the long-acting nitrates are as effective as sublingual nitroglycerin for the acute relief of angina. These organic nitrate preparations can be swallowed, chewed, or administered as a patch or paste by the transdermal route (Table 39-4). They can provide effective plasma levels for up to 24 h, but the therapeutic response is highly variable. Different preparations and/or administration during the daytime should be tried only to prevent discomfort while avoiding side effects such as headache and dizziness. Individual dose titration is important to prevent side effects. To minimize the effects of tolerance, the minimum effective dose should be used and a minimum of 8 h each day kept free of the drug to restore any useful response(s).

β-Adrenergic Blockers These drugs represent an important component of the pharmacologic treatment of angina pectoris (**Table 39-5**). They reduce myocardial oxygen demand by inhibiting the increases in heart rate, arterial pressure, and myocardial contractility caused by adrenergic activation. Beta blockade reduces these variables most strikingly during exercise but causes only small reductions at rest. Long-acting beta-blocking drugs or sustained-release formulations offer the advantage of once-daily dosing (Table 39-5). The therapeutic aims include relief of angina and ischemia. These drugs also can reduce mortality and reinfarction rates in patients after myocardial infarction and are moderately effective anti-hypertensive agents.

Relative contraindications include asthma and reversible airway obstruction in patients with chronic lung disease, atrioventricular conduction disturbances, severe bradycardia, Raynaud's phenomenon, and a history of mental depression. Side effects include fatigue, reduced exercise tolerance, nightmares, impotence, cold extremities, intermittent claudication, bradycardia (sometimes severe), impaired atrioventricular conduction, left ventricular failure, bronchial asthma, worsening claudication, and intensification of the hypoglycemia produced by oral hypoglycemic agents and insulin. Reducing the dose or even discontinuation may be necessary if these side effects develop and persist. Since sudden discontinuation can intensify ischemia, the doses should be tapered over 2 weeks. Beta blockers with relative β₁-receptor specificity such as metoprolol and atenolol may be preferable in patients with mild bronchial obstruction and insulin-requiring diabetes mellitus.

Calcium Channel Blockers Calcium channel blockers (Table 39-6) are coronary vasodilators that produce variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. These combined pharmacologic effects are advantageous and make these agents as effective as beta blockers in the treatment of angina pectoris. They are indicated when beta blockers are contraindicated, poorly tolerated, or ineffective. Because of differences in the dose-response relationship on cardiac electrical activity between the dihydropyridine and nondihydropyridine calcium channel blockers, verapamil and diltiazem may produce symptomatic

TABLE 39-5

PROPERTIES OF BETA BLOCKERS IN CLINICAL USE FOR ISCHEMIC HEART DISEASE			
DRUGS	SELECTIVITY	PARTIAL AGONIST ACTIVITY	USUAL DOSE FOR ANGINA
Acebutolol	β ₁	Yes	200–600 mg twice daily
Atenolol	β ₁	No	50–200 mg/d
Betaxolol	β ₁	No	10–20 mg/d
Bisoprolol	β ₁	No	10 mg/d
Esmolol (intravenous) ^a	β ₁	No	50–300 μg/kg/min
Labetalol ^b	None	Yes	200–600 mg twice daily
Metoprolol	β ₁	No	50–200 mg twice daily
Nadolol	None	No	40–80 mg/d
Nebivolol	β ₁ (at low doses)	No	5–40 mg/d
Pindolol	None	Yes	2.5–7.5 mg 3 times daily
Propranolol	None	No	80–120 mg twice daily
Timolol	None	No	10 mg twice daily

^aEsmolol is an ultra-short-acting beta blocker that is administered as a continuous intravenous infusion. Its rapid onset of action makes esmolol an attractive agent to use in patients with relative contraindications to beta blockade.

^bLabetalol is a combined alpha and beta blocker.

Note: This list of beta blockers that may be used to treat patients with angina pectoris is arranged alphabetically. The agents for which there is the greatest clinical experience include atenolol, metoprolol, and propranolol. It is preferable to use a sustained-release formulation that may be taken once daily to improve the patient's compliance with the regimen.

Source: Modified from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

TABLE 39-6

CALCIUM CHANNEL BLOCKERS IN CLINICAL USE FOR ISCHEMIC HEART DISEASE			
DRUGS	USUAL DOSE	DURATION OF ACTION	SIDE EFFECTS
Dihydropyridines			
Amlodipine	5–10 mg qd	Long	Headache, edema
Felodipine	5–10 mg qd	Long	Headache, edema
Isradipine	2.5–10 mg bid	Medium	Headache, fatigue
Nicardipine	20–40 mg tid	Short	Headache, dizziness, flushing, edema
Nifedipine	Immediate release: ^a 30–90 mg daily orally	Short	Hypotension, dizziness, flushing, nausea, constipation, edema
	Slow release: 30–180 mg orally		
Nisoldipine	20–40 mg qd	Short	Similar to nifedipine
Nondihydropyridines			
Diltiazem	Immediate release: 30–80 mg 4 times daily	Short	Hypotension, dizziness, flushing, bradycardia, edema
	Slow release: 120–320 mg qd	Long	
Verapamil	Immediate release: 80–160 mg tid	Short	Hypotension, myocardial depression, heart failure, edema, bradycardia
	Slow release: 120–480 mg qd	Long	

^aMay be associated with increased risk of mortality if administered during acute myocardial infarction.

Note: This list of calcium channel blockers that may be used to treat patients with angina pectoris is divided into two broad classes, dihydropyridines and nondihydropyridines, and arranged alphabetically within each class. Among the dihydropyridines, the greatest clinical experience has been obtained with amlodipine and nifedipine. After the initial period of dose titration with a short-acting formulation, it is preferable to switch to a sustained-release formulation that may be taken once daily to improve patient compliance with the regimen.

Source: Modified from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

disturbances in cardiac conduction and bradyarrhythmias. They also exert negative inotropic actions and are more likely to aggravate left ventricular failure, particularly when used in patients with left ventricular dysfunction, especially if the patients are also receiving beta blockers. Although useful effects usually are achieved when calcium channel blockers are combined with beta blockers and nitrates, individual titration of the doses is essential with these combinations. Variant (Prinzmetal's) angina responds particularly well to calcium channel blockers (especially members of the dihydropyridine class), supplemented when necessary by nitrates (**Chap. 40**).

Verapamil ordinarily should not be combined with beta blockers because of the combined adverse effects on heart rate and contractility. Diltiazem can be combined with beta blockers in patients with normal ventricular function and no conduction disturbances. Amlodipine and beta blockers have complementary actions on coronary blood supply and myocardial oxygen demands. Whereas the former decreases blood pressure and dilates coronary arteries, the latter slows heart rate and decreases contractility. Amlodipine and the other second-generation dihydropyridine calcium antagonists (nicardipine, isradipine, long-acting nifedipine, and felodipine) are potent vasodilators and are useful in the simultaneous treatment of angina and hypertension. Short-acting dihydropyridines should be avoided because of the risk of precipitating infarction, particularly in the absence of concomitant beta blocker therapy.

Choice Between Beta Blockers and Calcium Channel Blockers for Initial Therapy Since beta blockers have been shown to improve life expectancy after acute myocardial infarction (**Chaps. 40 and 41**) and calcium channel blockers have not, the former may also be preferable in patients with angina and a damaged left ventricle. However, calcium channel blockers are indicated in patients with the following: (1) inadequate responsiveness to the combination of beta blockers and nitrates; many of these patients do well with a combination of a beta blocker and a dihydropyridine calcium channel blocker; (2) adverse reactions to beta blockers such as depression, sexual disturbances, and fatigue; (3) angina and a history of asthma or chronic obstructive pulmonary disease; (4) sick-sinus syndrome or significant atrioventricular conduction disturbances; (5) Prinzmetal's angina; or (6) symptomatic peripheral arterial disease.

Antiplatelet Drugs Aspirin is an irreversible inhibitor of platelet cyclooxygenase and thereby interferes with platelet activation. Chronic administration of 75–325 mg orally per day has been shown to reduce coronary events in asymptomatic adult men over age 50, patients with chronic stable angina, and patients who have or have survived unstable angina and myocardial infarction. There is a dose-dependent increase in bleeding when aspirin is used chronically. It is preferable to use an enteric-coated formulation in the range of 81–162 mg/d. Administration of this drug should be considered in all patients with IHD in the absence of gastrointestinal bleeding, allergy, or dyspepsia. Clopidogrel (300–600 mg loading and 75 mg/d) is an oral agent that blocks P2Y₁₂ ADP receptor-mediated platelet

aggregation. It provides benefits similar to those of aspirin in patients with stable chronic IHD and may be substituted for aspirin if aspirin causes the side effects listed above. Clopidogrel combined with aspirin reduces death and coronary ischemic events in patients with an acute coronary syndrome (**Chap. 40**) and also reduces the risk of thrombus formation in patients undergoing implantation of a stent in a coronary artery (**Chap. 42**). Alternative antiplatelet agents that block the P2Y₁₂ platelet receptor such as prasugrel and ticagrelor have been shown to be more effective than clopidogrel for prevention of ischemic events after placement of a stent for an acute coronary syndrome but are associated with an increased risk of bleeding. Although combined treatment with clopidogrel and aspirin for at least a year is recommended in patients with an acute coronary syndrome treated with implantation of a drug-eluting stent, studies have not shown any benefit from the routine addition of clopidogrel to aspirin in patients with chronic stable IHD.

OTHER THERAPIES The angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of survivors of myocardial infarction, patients with hypertension or chronic IHD including angina pectoris, and those at high risk of vascular diseases such as diabetes. The benefits of ACE inhibitors are most evident in IHD patients at increased risk, especially if diabetes mellitus or left ventricle dysfunction is present, and those who have not achieved adequate control of blood pressure and LDL cholesterol on beta blockers and statins. However, the routine administration of ACE inhibitors to IHD patients who have normal left ventricular function and have achieved blood pressure and LDL goals on other therapies does not reduce the incidence of events and therefore is not cost-effective.

Despite treatment with nitrates, beta blockers, or calcium channel blockers, some patients with IHD continue to experience angina, and additional medical therapy is now available to alleviate their symptoms. Ranolazine, a piperazine derivative, may be useful for patients with chronic angina despite standard medical therapy. Its antianginal action is believed to occur via inhibition of the late inward sodium current (I_{Na}). The benefits of I_{Na} inhibition include limitation of the Na overload of ischemic myocytes and prevention of Ca^{2+} overload via the Na^+-Ca^{2+} exchanger. A dose of 500–1000 mg orally twice daily is usually well tolerated. Ranolazine is contraindicated in patients with hepatic impairment or with conditions or drugs associated with QT_c prolongation and when drugs that inhibit the CYP3A metabolic system (e.g., ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and large quantities of grapefruit juice) are being used.

Nonsteroidal anti-inflammatory drug (NSAID) use in patients with IHD may be associated with a small but finite increased risk of myocardial infarction and mortality. For this reason, they generally should be avoided in IHD patients. If they are required for symptom relief, it is advisable to coadminister aspirin and strive to use an NSAID associated with

456 the lowest risk of cardiovascular events, in the lowest dose required, and for the shortest period of time.

Another class of agents opens ATP-sensitive potassium channels in myocytes, leading to a reduction of free intracellular calcium ions. The major drug in this class is nicorandil, which typically is administered orally in a dose of 20 mg twice daily for prevention of angina. (Nicorandil is not available for use in the United States but is used in several other countries.)

Angina and Heart Failure Transient left ventricular failure with angina can be controlled by the use of nitrates. For patients with established congestive heart failure, the increased left ventricular wall tension raises myocardial oxygen demand. Treatment of congestive heart failure with an ACE inhibitor, a diuretic, and digoxin (**Chap. 19**) reduces heart size, wall tension, and myocardial oxygen demand, which helps control angina and ischemia. If the symptoms and signs of heart failure are controlled, an effort should be made to use beta blockers not only for angina but because trials in heart failure have shown significant improvement in survival. A trial of the intravenous ultra-short-acting beta blocker esmolol may be useful to establish the safety of beta blockade in selected patients. Nocturnal angina often can be relieved by the treatment of heart failure.

The combination of congestive heart failure and angina in patients with IHD usually indicates a poor prognosis and warrants serious consideration of cardiac catheterization and coronary revascularization.

CORONARY REVASCULARIZATION

Clinical trials have confirmed that with the initial diagnosis of stable IHD, it is first appropriate to initiate a thorough medical regimen as described above. Revascularization should be considered in the presence of unstable phases of the disease, intractable symptoms, severe ischemia or high-risk coronary anatomy, diabetes, and impaired left ventricular (LV) function. Revascularization should be employed in conjunction with but not replace the continuing need to modify risk factors and assess medical therapy. An algorithm for integrating medical therapy and revascularization options in patients with IHD is shown in Fig. 39-3.

PERCUTANEOUS CORONARY INTERVENTION

(See also **Chap. 42**) Percutaneous coronary intervention (PCI) involving balloon dilatation usually accompanied by coronary stenting is widely used to achieve revascularization of the myocardium in patients with symptomatic IHD and suitable stenoses of epicardial coronary arteries. Whereas patients with stenosis of the

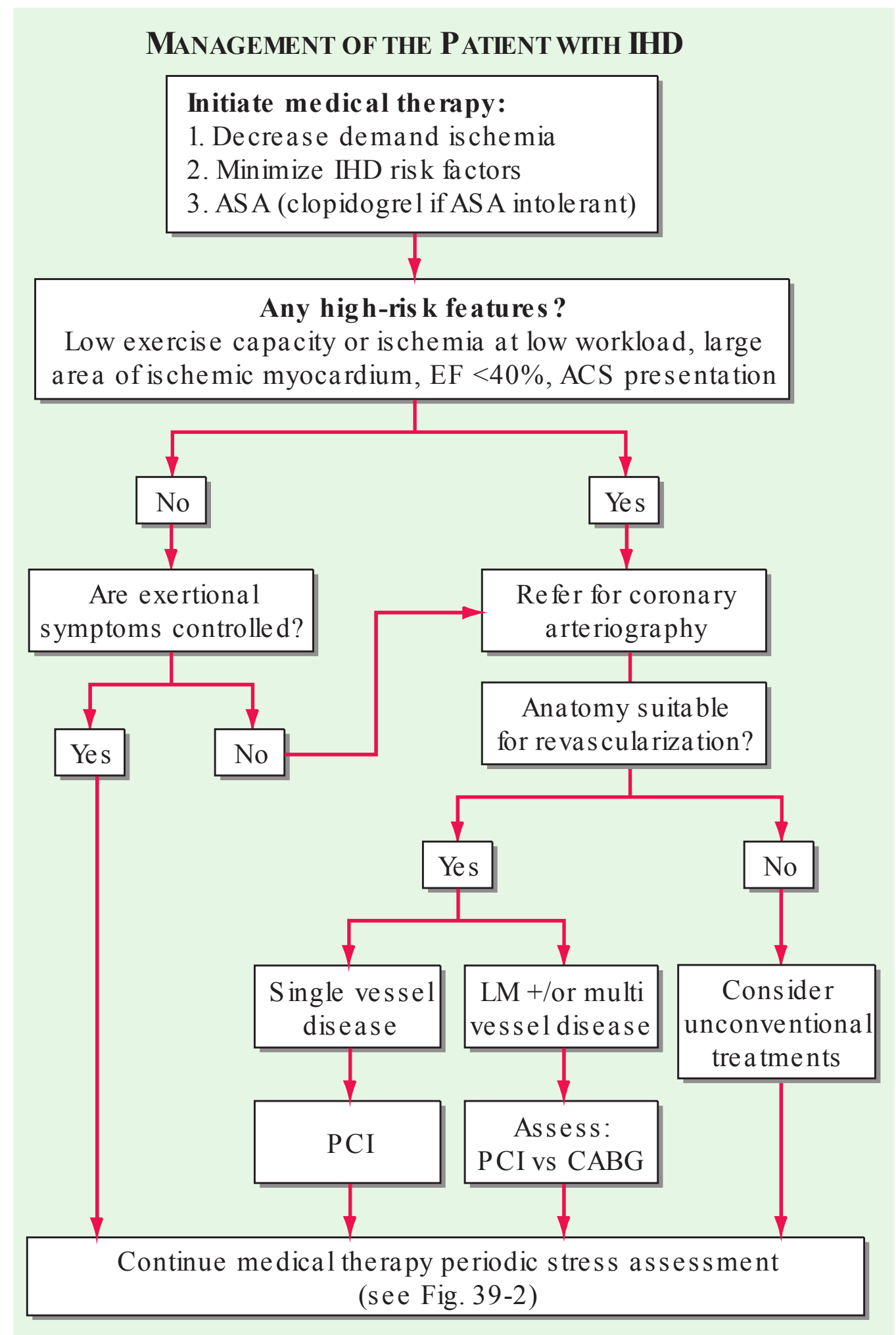


FIGURE 39-3

Algorithm for management of a patient with ischemic heart disease. All patients should receive the core elements of medical therapy as shown at the top of the algorithm. If high-risk features are present, as established by the clinical history, exercise test data, and imaging studies, the patient should be referred for coronary arteriography. Based on the number and location of the diseased vessels and their suitability for revascularization, the patient is treated with a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or should be considered for unconventional treatments. See text for further discussion. ACS, acute coronary syndrome; ASA, aspirin; EF, ejection fraction; IHD, ischemic heart disease; LM, left main.

left main coronary artery and those with three-vessel IHD (especially with diabetes and/or impaired LV function) who require revascularization are best treated with CABG, PCI is widely employed in patients with symptoms and evidence of ischemia due to stenoses of one or two vessels and even in selected patients with three-vessel disease (and, perhaps, in some patients with left main disease) and may offer many advantages over surgery.

Indications and patient selection

The most common clinical indication for PCI is symptom-limiting angina pectoris, despite medical therapy, accompanied by evidence of ischemia during a stress test. PCI is more effective than medical therapy for the relief of angina. PCI improves outcomes in patients with unstable angina or when used early in the course of myocardial infarction with and without cardiogenic shock. However, in patients with stable exertional angina, clinical trials have confirmed that PCI does not reduce the occurrence of death or myocardial infarction compared to optimum medical therapy. PCI can be used to treat stenoses in native coronary arteries as well as in bypass grafts in patients who have recurrent angina after CABG.

Risks

When coronary stenoses are discrete and symmetric, two and even three vessels can be treated in sequence. However, case selection is essential to avoid a prohibitive risk of complications, which are usually due to dissection or thrombosis with vessel occlusion, uncontrolled ischemia, and ventricular failure (**Chap. 42**). Oral aspirin, a P2Y₁₂ antagonist, and an antithrombin agent are given to reduce coronary thrombus formation. Left main coronary artery stenosis generally is regarded as a contraindication to PCI; such patients should be treated with CABG. In selected cases such as patients with prohibitive surgical risks, PCI of an unprotected left main can be considered, but such a procedure should be performed only by a highly skilled operator; importantly, there are regional differences in the use of this approach internationally.

Efficacy

Primary success, i.e., adequate dilation (an increase in luminal diameter >20% to a residual diameter obstruction <50%) with relief of angina, is achieved in >95% of cases. Recurrent stenosis of the dilated vessels occurs in □20% of cases within 6 months of PCI with bare metal stents, and angina will recur within 6 months in 10% of cases. Restenosis is more common in patients with diabetes mellitus, arteries with small caliber, incomplete dilation of the stenosis, long stents, occluded vessels, obstructed vein grafts, dilation of the left anterior descending coronary artery, and stenoses containing thrombi. In diseased vein grafts, procedural success has been improved by the use of capture devices or filters that prevent embolization, ischemia, and infarction.

It is usual clinical practice to administer aspirin indefinitely and a P2Y₁₂ antagonist for 1–3 months after the implantation of a bare metal stent. Although aspirin in combination with a thienopyridine may help prevent coronary thrombosis during and shortly after

PCI with stenting, there is no evidence that these medications reduce the incidence of restenosis.

The use of drug-eluting stents that locally deliver antiproliferative drugs can reduce restenosis to less than 10%. Advances in PCI, especially the availability of drug-eluting stents, have vastly extended the use of this revascularization option in patients with IHD. Of note, however, the delayed endothelial healing in the region of a drug-eluting stent also extends the period during which the patient is at risk for subacute stent thrombosis. Current recommendations are to administer aspirin indefinitely and a P2Y₁₂ antagonist daily for at least 1 year after implantation of a drug-eluting stent. When a situation arises in which temporary discontinuation of antiplatelet therapy is necessary, the clinical circumstances should be reviewed with the operator who performed the PCI and a coordinated plan should be established for minimizing the risk of late stent thrombus; central to this plan is the discontinuation of antiplatelet therapy for the shortest acceptable period. The risk of stent thrombosis is dependent on stent size and length, complexity of the lesions, age, diabetes, and technique. However, compliance with dual antiplatelet therapy and individual responsiveness to platelet inhibition are very important factors as well.

Successful PCI produces effective relief of angina in >95% of cases. The majority of patients with symptomatic IHD who require revascularization can be treated initially by PCI. Successful PCI is less invasive and expensive than CABG and permits savings in the initial cost of care. Successful PCI avoids the risk of stroke associated with CABG surgery, allows earlier return to work, and allows the resumption of an active life. However, the early health-related and economic benefit of PCI is reduced over time because of the greater need for follow-up and the increased need for repeat procedures. When directly compared in patients with diabetes or three-vessel or left main CAD, CABG was superior to PCI in preventing major adverse cardiac or cerebrovascular events over a 12-month follow-up.

CORONARY ARTERY BYPASS GRAFTING

Anastomosis of one or both of the internal mammary arteries or a radial artery to the coronary artery distal to the obstructive lesion is the preferred procedure. For additional obstructions that cannot be bypassed by an artery, a section of a vein (usually the saphenous) is used to form a connection between the aorta and the coronary artery distal to the obstructive lesion.

Although some indications for CABG are controversial, certain areas of agreement exist:

1. The operation is relatively safe, with mortality rates <1% in patients without serious comorbid disease and normal LV function and when the procedure is performed by an experienced surgical team.

2. Intraoperative and postoperative mortality rates increase with the severity of ventricular dysfunction, comorbidities, age >80 years, and lack of surgical experience. The effectiveness and risk of CABG vary widely depending on case selection and the skill and experience of the surgical team.
3. Occlusion of venous grafts is observed in 10–20% of patients during the first postoperative year and in approximately 2% per year during 5- to 7-year follow-up and 4% per year thereafter. Long-term patency rates are considerably higher for internal mammary and radial artery implantations than for saphenous vein grafts. In patients with left anterior descending coronary artery obstruction, survival is better when coronary bypass involves the internal mammary artery rather than a saphenous vein. Graft patency and outcomes are improved by meticulous treatment of risk factors, particularly dyslipidemia.
4. Angina is abolished or greatly reduced in ~90% of patients after complete revascularization. Although this usually is associated with graft patency and restoration of blood flow, the pain may also have been alleviated as a result of infarction of the ischemic segment or a placebo effect. Within 3 years, angina recurs in about one-fourth of patients but is rarely severe.
5. Survival may be improved by operation in patients with stenosis of the left main coronary artery as well as in patients with three- or two-vessel disease with significant obstruction of the proximal left anterior descending coronary artery. The survival benefit is greater in patients with abnormal LV function (ejection fraction <50%). Survival may also be improved in the following patients: (a) patients with obstructive CAD who have survived sudden cardiac death or sustained ventricular tachycardia; (b) patients who have undergone previous CABG and have multiple saphenous vein graft stenoses, especially of a graft supplying the left anterior descending coronary artery; and (c) patients with recurrent stenosis after PCI and high-risk criteria on noninvasive testing.
6. Minimally invasive CABG through a small thoracotomy and/or of -pump surgery can reduce morbidity and shorten convalescence in suitable patients but does not appear to reduce significantly the risk of neurocognitive dysfunction postoperatively.
7. Among patients with type 2 diabetes mellitus and multivessel coronary disease, CABG surgery plus optimal medical therapy is superior to optimal medical therapy alone in preventing major cardiovascular events, a benefit mediated largely by a significant reduction in nonfatal myocardial infarction. The benefits of CABG are especially evident in diabetic patients treated with an insulin-sensitizing strategy

as opposed to an insulin-providing strategy. CABG has also been shown to be superior to PCI (including the use of drug-eluting stents) in preventing death, myocardial infarction, and repeat revascularization in patients with diabetes mellitus and multivessel IHD.

Indications for CABG usually are based on the severity of symptoms, coronary anatomy, and ventricular function. The ideal candidate is male, <80 years of age, has no other complicating disease, and has troublesome or disabling angina that is not adequately controlled by medical therapy or does not tolerate medical therapy. The patient wishes to lead a more active life and has severe stenoses of two or three epicardial coronary arteries with objective evidence of myocardial ischemia as a cause of the chest discomfort. Great symptomatic benefit can be anticipated in such patients. Congestive heart failure and/or LV dysfunction, advanced age (>80 years), reoperation, urgent need for surgery, and the presence of diabetes mellitus are all associated with a higher perioperative mortality rate.

LV dysfunction can be due to noncontractile or hypocontractile segments that are viable but are chronically ischemic (hibernating myocardium). As a consequence of chronic reduction in myocardial blood flow, these segments downregulate their contractile function. They can be detected by using radionuclide scans of myocardial perfusion and metabolism, PET, cardiac MRI, or delayed scanning with thallium-201 or by improvement of regional functional impairment provoked by low-dose dobutamine. In such patients, revascularization improves myocardial blood flow, can return function, and can improve survival.

The choice between PCI and CABG

All the clinical characteristics of each individual patient must be used to decide on the method of revascularization (e.g., LV function, diabetes, lesion complexity). A number of randomized clinical trials have compared PCI and CABG in patients with multivessel CAD who were suitable technically for both procedures. The redevelopment of angina requiring repeat coronary angiography and repeat revascularization is higher with PCI. This is a result of restenosis in the stented segment (a problem largely solved with drug-eluting stents) and the development of new stenoses in unstented portions of the coronary vasculature. It has been argued that PCI with stenting focuses on culprit lesions, whereas a bypass graft to the target vessel also provides a conduit around future culprit lesions proximal to the anastomosis of the graft to the native vessel (Fig. 39-4). By contrast, stroke rates are lower with PCI.

Based on available evidence, it is now recommended that patients with an unacceptable level of angina despite optimal medical management be considered

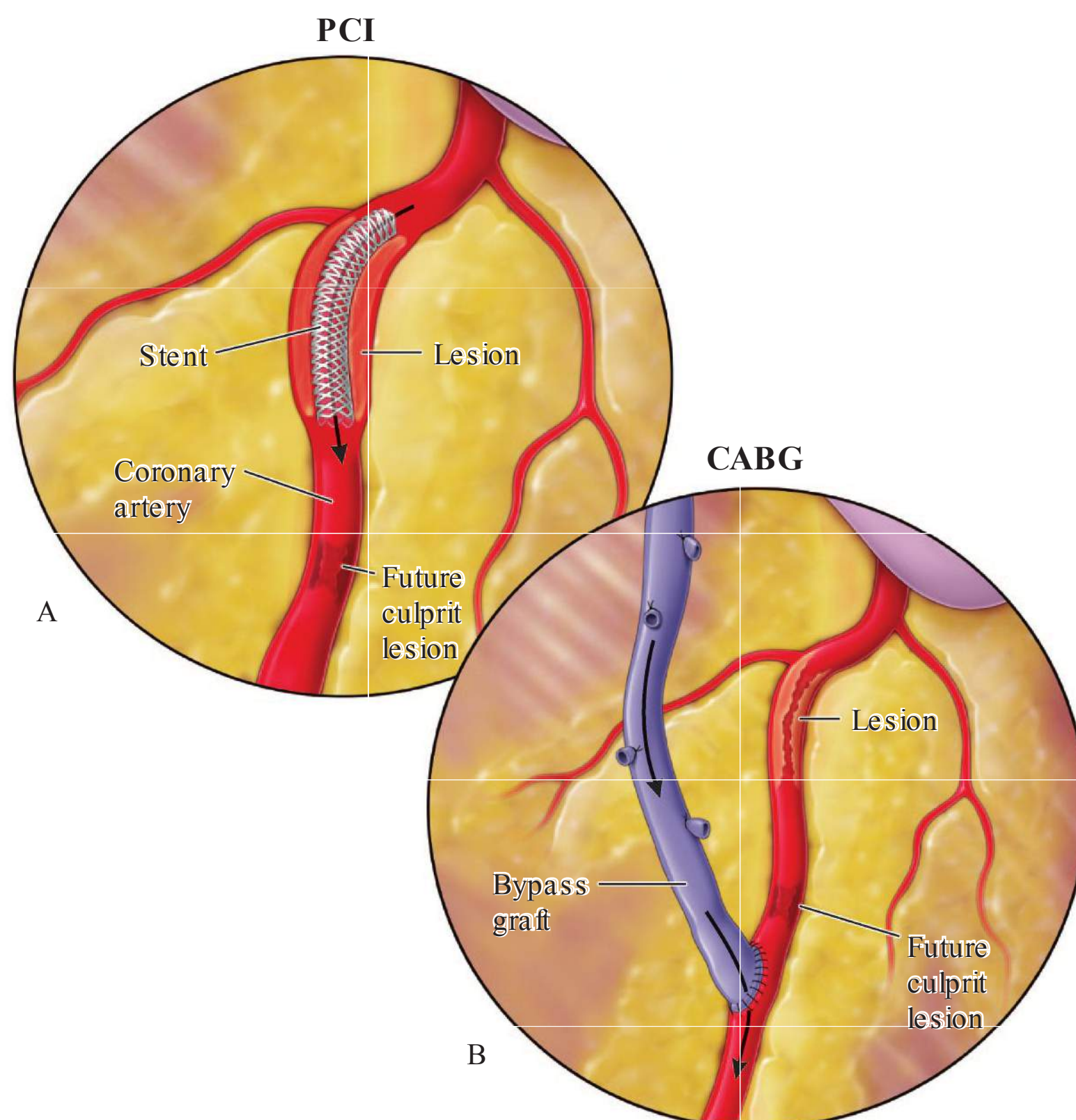


FIGURE 39-4

Difference in the approach to the lesion with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). PCI is targeted at the “culprit” lesion or lesions, whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions and future culprits, proximal to the insertion of

the vein graft, a difference that may account for the superiority of CABG, at least in the intermediate term, in patients with multivessel disease. (Reproduced from BJ Gersh, RL Frye: *N Engl J Med* 352:2235, 2005.)

for coronary revascularization. Patients with single- or two-vessel disease with normal LV function and anatomically suitable lesions ordinarily are advised to undergo PCI (**Chap. 42**). Patients with three-vessel disease (or two-vessel disease that includes the proximal left descending coronary artery) and impaired global LV function (LV ejection fraction $<50\%$) or diabetes mellitus and those with left main CAD or other lesions unsuitable for catheter-based procedures should be considered for CABG as the initial method of revascularization. In light of the complexity of the decision making, it is desirable to have a multidisciplinary team, including a cardiologist and a cardiac surgeon in conjunction with the patient’s primary care physician, provide input along with ascertaining the patient’s preferences before committing to a particular revascularization option.

UNCONVENTIONAL TREATMENTS FOR IHD

On occasion clinicians will encounter a patient who has persistent disabling angina despite maximally tolerated medical therapy and for whom revascularization is

not an option (e.g., small diffusely diseased vessels not amenable to stent implantation or acceptable targets for bypass grafting). In such situations, unconventional treatments should be considered.

Enhanced external counterpulsation utilizes pneumatic cuffs on the lower extremities to provide diastolic augmentation and systolic unloading of blood pressure to decrease cardiac work and oxygen consumption while enhancing coronary blood flow. Clinical trials have shown that regular application improves angina, exercise capacity, and regional myocardial perfusion. Experimental approaches such as gene and stem cell therapies are also under active study.

ASYMPTOMATIC (SILENT) ISCHEMIA

Obstructive CAD, acute myocardial infarction, and transient myocardial ischemia are frequently asymptomatic. During continuous ambulatory ECG monitoring, the majority of ambulatory patients with typical chronic stable angina are found to have objective

evidence of myocardial ischemia (ST-segment depression) during episodes of chest discomfort while they are active outside the hospital. In addition, many of these patients also have more frequent episodes of asymptomatic ischemia. Frequent episodes of ischemia (symptomatic and asymptomatic) during daily life appear to be associated with an increased likelihood of adverse coronary events (death and myocardial infarction). In addition, patients with asymptomatic ischemia after a myocardial infarction are at greater risk for a second coronary event. The widespread use of exercise ECG during routine examinations has also identified some of these previously unrecognized patients with asymptomatic CAD. Longitudinal studies have demonstrated an increased incidence of coronary events in asymptomatic patients with positive exercise tests.

TREATMENT Asymptomatic Ischemia

The management of patients with asymptomatic ischemia must be individualized. When coronary disease has been confirmed, the aggressive treatment of hypertension and dyslipidemia is essential and will decrease the risk of infarction and death. In addition, the physician should consider the following: (1) the degree of positivity of the stress test, particularly the stage of exercise at which ECG signs of ischemia appear; the magnitude and number of the ischemic zones of

myocardium on imaging; and the change in LV ejection fraction that occurs on radionuclide ventriculography or echocardiography during ischemia and/or during exercise; (2) the ECG leads showing a positive response, with changes in the anterior precordial leads indicating a less favorable prognosis than changes in the inferior leads; and (3) the patient's age, occupation, and general medical condition.

Most would agree that an asymptomatic 45-year-old commercial airline pilot with significant (0.4-mV) ST-segment depression in leads V_1 to V_4 during mild exercise should undergo coronary arteriography, whereas an asymptomatic, sedentary 85-year-old retiree with 0.1-mV ST-segment depression in leads II and III during maximal activity need not. However, there is no consensus about the most appropriate approach in the large majority of patients for whom the situation is less extreme. Asymptomatic patients with silent ischemia, three-vessel CAD, and impaired LV function may be considered appropriate candidates for CABG.

The treatment of risk factors, particularly lipid lowering and blood pressure control as described above, and the use of aspirin, statins, and beta blockers after infarction have been shown to reduce events and improve outcomes in asymptomatic as well as symptomatic patients with ischemia and proven CAD. Although the incidence of asymptomatic ischemia can be reduced by treatment with beta blockers, calcium channel blockers, and long-acting nitrates, it is not clear whether this is necessary or desirable in patients who have not had a myocardial infarction.

CHAPTER 40

NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME (NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION AND UNSTABLE ANGINA)



Christopher P. Cannon ■ Eugene Braunwald

Patients with ischemic heart disease fall into two large groups: patients with chronic coronary artery disease (CAD) who most commonly present with stable angina (**Chap. 39**) and patients with acute coronary syndromes (ACSs). These include patients with acute myocardial infarction with ST-segment elevation (STEMI) on their presenting electrocardiogram (**Chap. 41**) and those with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS). The latter include patients with non-ST-segment elevation myocardial infarction (NSTEMI), who, by definition, have evidence of myocyte necrosis, and those with unstable angina (UA), who do not. The relative incidence of NSTEMI compared to STEMI appears to be increasing (**Fig. 40-1**). Every year in the United States, approximately 1.1 million patients are admitted to hospitals with NSTEMI-ACS as compared with ~300,000 patients with acute STEMI. Women comprise more than one-third of patients with NSTEMI-ACS, but less than one-fourth of patients with STEMI.

PATHOPHYSIOLOGY

NSTEMI-ACS is most commonly caused by an imbalance between oxygen supply and oxygen demand resulting from a partially occluding thrombus forming on a disrupted atherothrombotic coronary plaque or on eroded coronary artery endothelium. Severe ischemia or myocardial necrosis may occur consequent to the reduction of coronary blood flow caused by the thrombus and by downstream embolization of platelet aggregates and/or atherosclerotic debris. Other causes of NSTEMI-ACS include: (1) dynamic obstruction

(e.g., coronary spasm, as in Prinzmetal's variant angina [see "Prinzmetal's Variant Angina" later]); (2) severe mechanical obstruction due to progressive coronary atherosclerosis; and (3) increased myocardial oxygen demand produced by conditions such as fever, tachycardia, and thyrotoxicosis in the presence of fixed epicardial coronary obstruction. More than one of these processes may be involved.

Among patients with NSTEMI-ACS studied at angiography, approximately 10% have stenosis of the left main coronary artery, 35% have three-vessel CAD, 20% have two-vessel disease, 20% have single-vessel disease, and 15% have no apparent critical epicardial coronary artery stenosis; some of the latter may have obstruction of the coronary microcirculation and/or spasm. The "culprit lesion" responsible for ischemia may show an eccentric stenosis with scalloped or overhanging edges and a narrow neck on coronary angiography. Optical coherence tomography (an invasive technique) and contrast-enhanced coronary computed tomographic angiography (CCTA), a noninvasive technique (**Fig. 40-2**), have shown that culprit lesions are composed of a lipid-rich core with a thin fibrous cap. Patients with NSTEMI-ACS frequently have multiple such plaques that are at risk of disruption (vulnerable plaques).

CLINICAL PRESENTATION

Diagnosis

The diagnosis of NSTEMI-ACS is based largely on the clinical presentation. Typically, chest discomfort is severe and has at least one of three features: (1) it occurs at rest (or with minimal exertion), lasting >10 minutes; (2) it is of

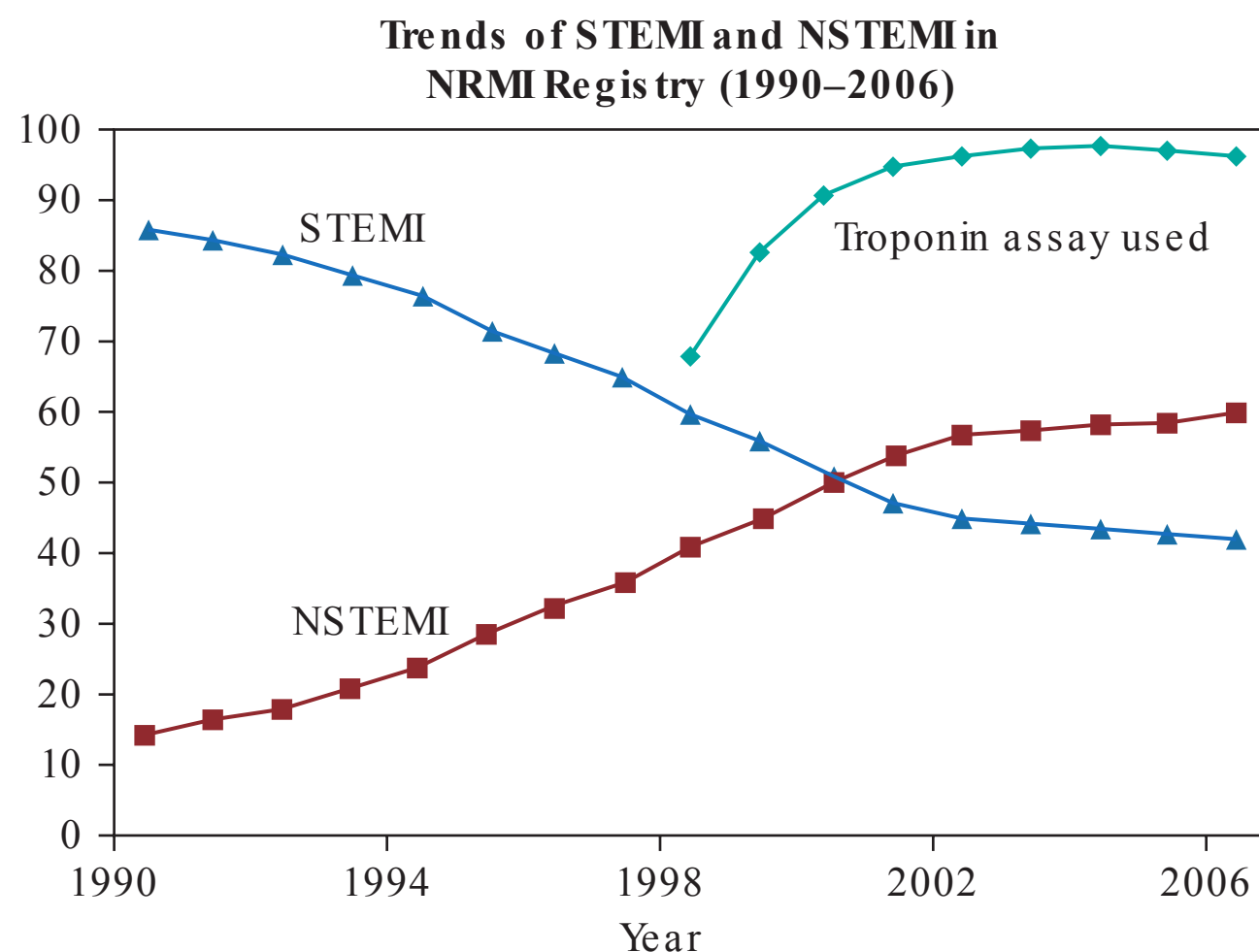


FIGURE 40-1

Trends of incidence of ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) and of frequency of use of troponin assay to diagnose acute myocardial infarction. NRMI, National Registry of Myocardial Infarction. (From N Arora, RG Brindis, CP Cannon: *Acute coronary syndrome in North America*, in Theroux P [ed]: *Acute Coronary Syndromes*, 2nd ed. Philadelphia: Elsevier, 2011.)

relatively recent onset (i.e., within the prior 2 weeks); and/or (3) it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previous episodes). The diagnosis of NSTEMI is established if a patient with these clinical features develops evidence of myocardial necrosis, as reflected in abnormally elevated levels of biomarkers of cardiac necrosis (see below).

History and physical examination

The chest discomfort, often severe enough to be described as frank pain, is typically located in the substernal region or sometimes in the epigastrium, and radiates to the left arm, left shoulder, and/or neck. Anginal “equivalents” such as dyspnea, epigastric discomfort, nausea, or weakness may occur instead of chest pain and appear to be more frequent in women, the elderly, and patients with diabetes mellitus. The physical examination resembles that in patients with stable angina (**Chap. 39**) and may be unremarkable. If the patient has a large area of myocardial ischemia or a large NSTEMI, the physical findings can include diaphoresis; pale, cool skin; sinus tachycardia; a third and/or fourth heart sound; basilar rales; and, sometimes, hypotension.

Electrocardiogram

ST-segment depression occurs in 20 to 25% of patients; it may be transient in patients without biomarker evidence of myocardial necrosis, but may be persistent for several days in NSTEMI. T-wave changes are common but are less specific signs of ischemia, unless they are new and deep T-wave inversions (≥ 0.3 mV).

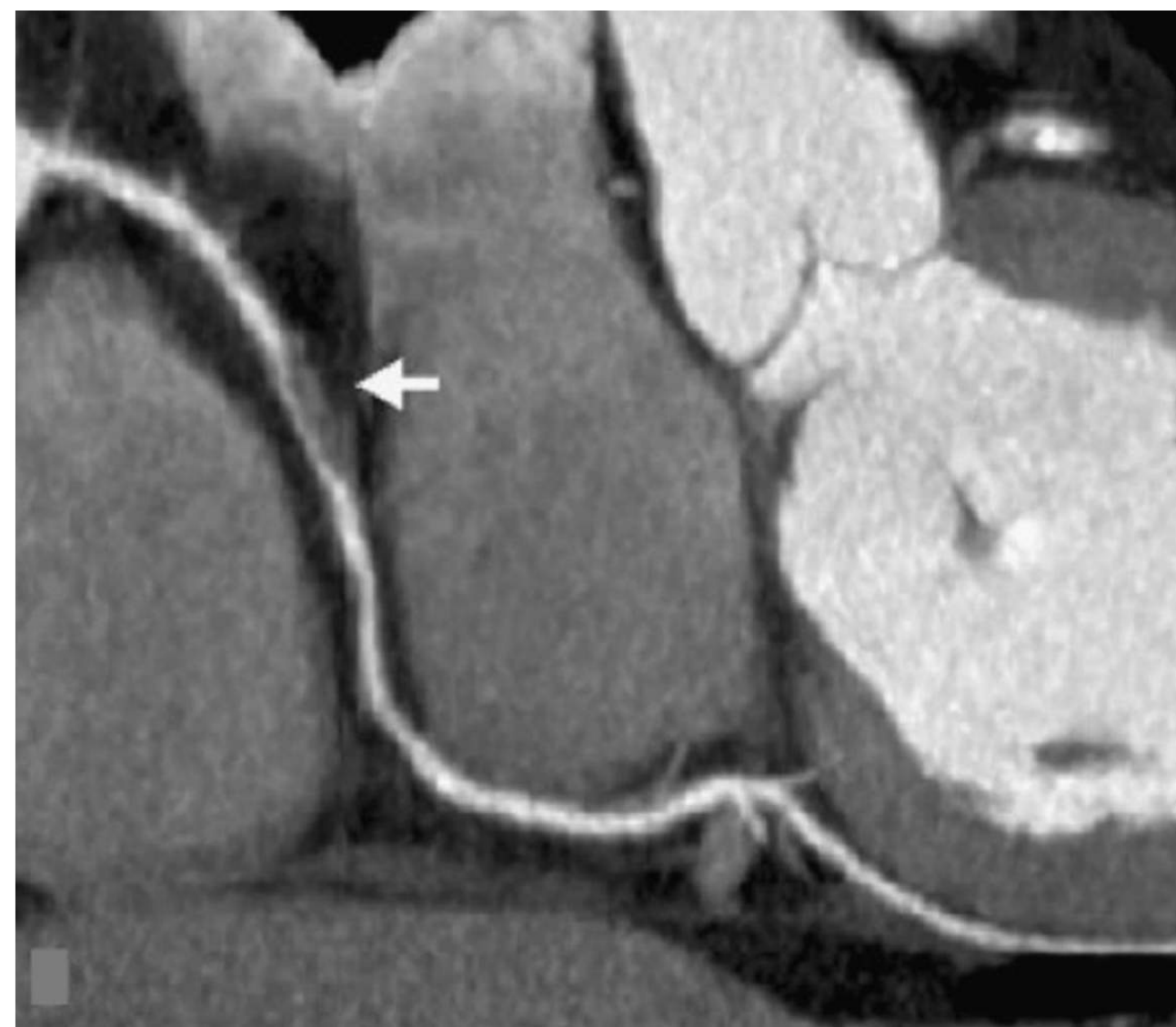


FIGURE 40-2

Coronary computed tomographic angiogram showing an obstructive plaque in the right coronary artery. (From PJ de Feyter, K Nieman. *Multislice computed tomography in acute coronary syndromes*, in Theroux P [ed]: *Acute Coronary Syndromes*, 2nd ed. Philadelphia: Elsevier, 2011.)

Cardiac biomarkers

Patients with NSTEMI have elevated biomarkers of necrosis, such as cardiac troponin I or T, which are specific, sensitive, and the preferred markers of myocardial necrosis. The MB isoform of creatine kinase (CK-MB) is a less sensitive alternative. Elevated levels of these markers distinguish patients with NSTEMI from those with UA. There is a characteristic temporal rise and fall of the plasma concentration of these markers and a direct relationship between the degree of elevation and mortality (see Fig. 40-4B). However, in patients without a clear clinical history of myocardial ischemia, minor cardiac troponin (cTn) elevations have been reported and can be caused by congestive heart failure, myocarditis, or pulmonary embolism, or using high-sensitivity assays, they may occur in ostensibly normal subjects. Thus, in patients with an unclear history, small elevations of cTn, especially if they are persistent, may not be diagnostic of an ACS.

With more widespread measurement of troponin, especially using high-sensitivity assays, an increasing fraction of patients with NSTEMI-ACS are found to have NSTEMI, whereas the fraction of patients with UA is dwindling.

DIAGNOSTIC EVALUATION

In addition to the clinical examination, three major noninvasive tools are used in the evaluation of NSTEMI-ACS: the electrocardiogram (ECG), cardiac biomarkers, and stress testing. CCTA is an additional

emerging option (Fig. 40-2). The goals are to: (1) recognize or exclude myocardial infarction (MI) using cardiac biomarkers, preferably cTn; (2) detect rest ischemia (using serial or continuous ECGs); and (3) detect significant coronary obstruction at rest with CCTA and myocardial ischemia using stress testing (**Chap 12**).

Patients with a low likelihood of ischemia are usually managed with an emergency department–based critical pathway (which, in some institutions, is carried out in a “chest pain unit”) (**Fig. 40-3**). Evaluation of such patients includes clinical monitoring for recurrent ischemic discomfort and continuous monitoring of ECGs and cardiac markers, typically obtained at baseline and at 4–6 h and 12 h after presentation. If new elevations in cardiac markers or ST-T-wave changes on the ECG are noted, the patient should be admitted to the hospital. Patients who remain pain free with negative markers may proceed to stress testing to determine the presence of ischemia or CCTA to detect coronary luminal obstruction (Fig. 40-2).

RISK STRATIFICATION

Patients with documented NSTEMI-ACS exhibit a wide spectrum of early (30 days) risk of death, ranging from 1 to 10%, and a recurrent ACS rate of 5 to 15% during

the first year. Assessment of risk can be accomplished by clinical risk scoring systems such as that developed from the Thrombolysis in Myocardial Infarction (TIMI) Trials, which includes seven independent risk factors (**Fig. 40-4A**). The presence of an abnormally elevated cTn is especially important, as is its peak level, which correlates with the extent of myocardial damage (**Fig. 40-4B**). Other risk factors include diabetes mellitus, left ventricular dysfunction, renal dysfunction, and elevated levels of B-type natriuretic peptides and C-reactive protein. Multimarker strategies are now gaining favor, both to define more fully the pathophysiologic mechanisms underlying a given patient’s presentation and to stratify the patient’s risk further. Patients with ACS without elevated levels of cTn (infrequently encountered with the new sensitive troponin assays) are considered to have UA and have a more favorable prognosis than those with cTn elevations (NSTEMI).

Early risk assessment is useful both in predicting the risk of recurrent cardiac events and in identifying patients who would derive the greatest benefit from an early invasive strategy. For example, in the TACTICS-TIMI 18 Trial, an early invasive strategy conferred a 40% reduction in recurrent cardiac events in patients with an elevated cTn level, whereas no benefit was observed in those without detectable troponin.

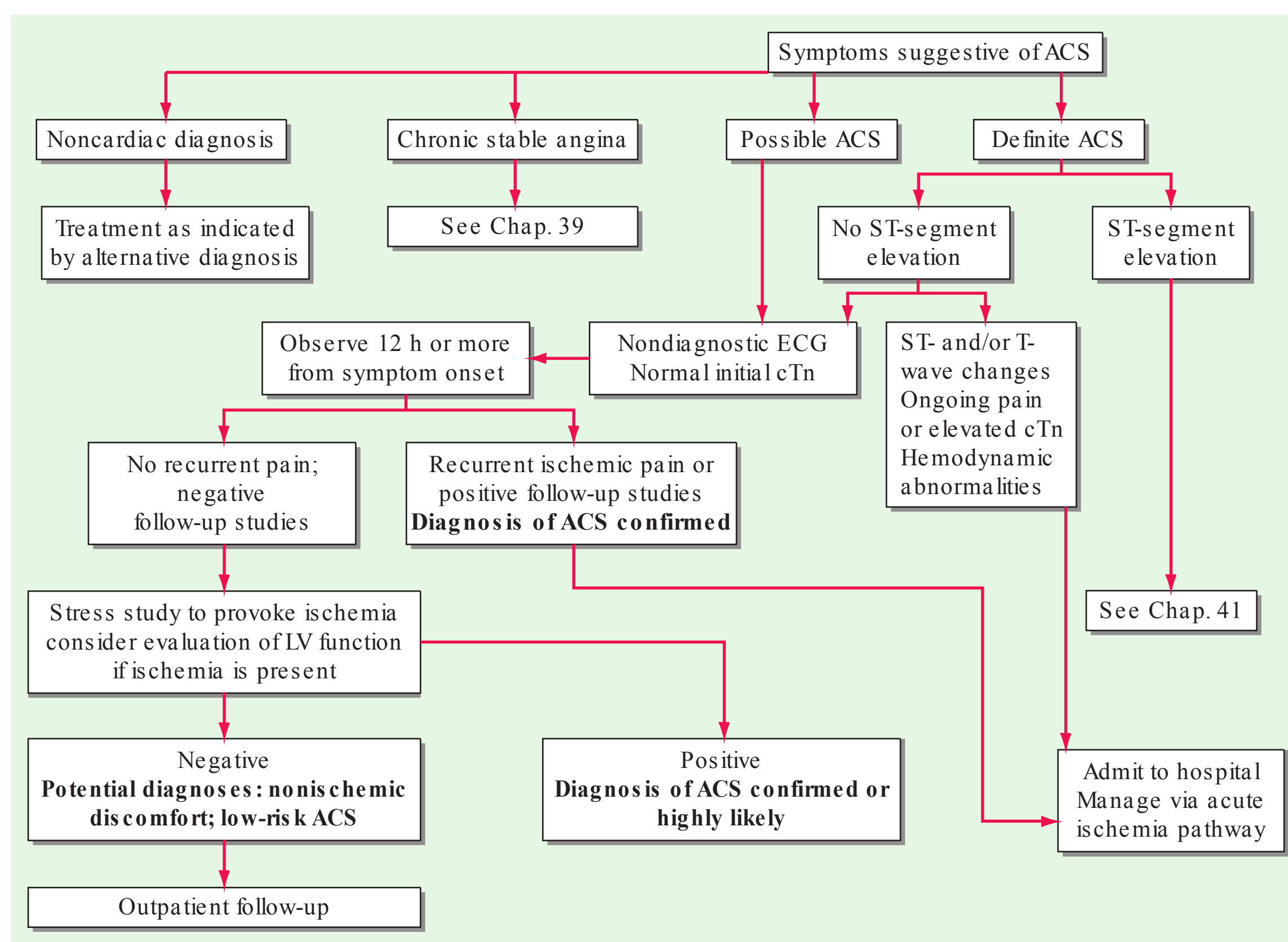


FIGURE 40-3

Algorithm for evaluation and management of patients with suspected acute coronary syndrome (ACS). Follow-up studies refer to ST deviations and elevation of troponin levels. cTn, cardiac troponin; ECG, electrocardiogram; LV, left ventricular. (Modified from J.L. Anderson et al: *J Am Coll Cardiol* 61:e179, 2013.)

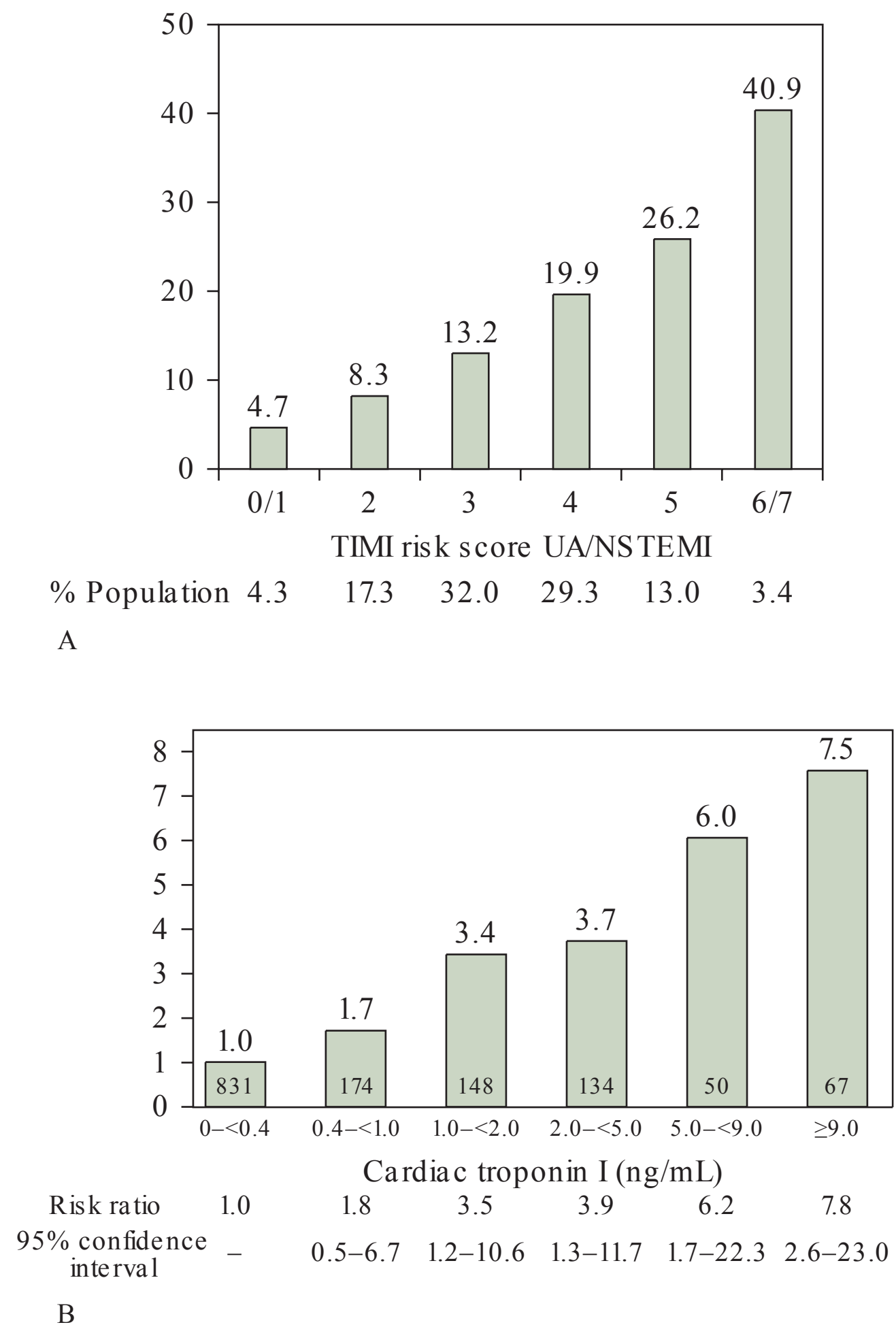


FIGURE 40-4
A. Death (D), myocardial infarction (MI), or need for urgent revascularization (UR) through 6 weeks by Thrombolysis in Myocardial Infarction (TIMI) Risk Score in the unfractionated heparin arm of the TIMI 11B trial. (From EM Antman et al: JAMA 284:835, 2000.) B. Mortality rate at 42 days by baseline cardiac troponin I levels in the TIMI 3B trial. (From EM Antman et al: N Engl J Med 335:1342, 1996.)

TREATMENT Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina)

MEDICAL TREATMENT Patients should be placed at bed rest with continuous ECG monitoring for ST-segment deviation and cardiac arrhythmias. Ambulation is permitted if the patient shows no recurrence of ischemia (symptoms or ECG changes) and does not develop an elevation of a biomarker of necrosis for 12–24 h. Medical therapy involves simultaneous anti-ischemic and antithrombotic treatments and consideration of coronary revascularization.

ANTI-ISCHEMIC TREATMENT To provide relief and prevention of recurrence of chest pain, initial treatment should include bed rest, nitrates, beta adrenergic blockers, and inhaled oxygen in

the presence of hypoxemia (**Table 40-1**).

Nitrates These should first be given sublingually or by buccal spray (0.3–0.6 mg) if the patient is experiencing ischemic pain. If pain persists after three doses given 5 min apart, intravenous nitroglycerin (5–10 µg/min using nonabsorbing tubing) is recommended. The rate of the infusion may be increased by 10 µg/min every 3–5 min until symptoms are relieved, systolic arterial pressure falls to <100 mmHg, or the dose reaches 200 µg/min. Topical or oral nitrates (**Chap. 39**) can be used when the pain has resolved, or they may replace intravenous nitroglycerin when the patient has been pain-free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension or the use of sildenafil or other phosphodiesterase-5 inhibitors within the previous 24–48 h.

Beta Adrenergic Blockers and Other Agents Beta blockers are the other mainstay of anti-ischemic treatment. They may be started by the intravenous route in patients with severe ischemia, but this is contraindicated in the presence of heart failure. Ordinarily, oral beta blockade targeted to a heart rate of 50–60 beats/min is recommended. Heart rate–slowing calcium channel blockers, e.g., verapamil or diltiazem, are recommended for patients who have persistent symptoms or ECG signs of ischemia after treatment with full-dose nitrates and beta blockers and in patients with contraindications to either class of these agents. Additional medical therapy includes angiotensin-converting enzyme (ACE) inhibitors or, if these are not tolerated, angiotensin receptor blockers. Early administration of intensive HMG-CoA reductase inhibitors (statins), such as atorvastatin 80 mg/d, prior to percutaneous coronary intervention (PCI), and continued thereafter, has been shown to reduce complications of the procedure and recurrences of ACS.

ANTI-THROMBOTIC THERAPY This is the second major cornerstone of treatment (**Table 40-2**). There are two components of antithrombotic therapy: antiplatelet drugs and anticoagulants.

Antiplatelet Drugs Initial treatment should begin with the platelet cyclooxygenase inhibitor aspirin. The typical initial dose is 325 mg/d, with lower doses (75–100 mg/d) recommended thereafter. Contraindications are active bleeding or aspirin intolerance. “Aspirin resistance” has been noted in 2–8% of patients but frequently has been related to noncompliance.

In the absence of a high risk for bleeding, patients with NSTEMI-ACS, irrespective of whether an invasive or conservative strategy (see below) is selected, should receive a platelet P2Y₁₂ receptor blocker to inhibit platelet activation. The thienopyridine clopidogrel is an inactive prodrug that is converted into an active metabolite that causes irreversible blockade of the platelet P2Y₁₂ receptor. When added to aspirin, so-called dual antiplatelet therapy, it has been shown to confer a 20% relative reduction in cardiovascular death, MI, or stroke, compared to aspirin alone, but to be associated with a moderate (absolute 1%) increase in major bleeding.

TABLE 40-1

DRUGS COMMONLY USED IN INTENSIVE MEDICAL MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

DRUG CATEGORY	CLINICAL CONDITION	WHEN TO AVOID ^a	DOSAGE
Nitrates	Administer sublingually, and, if symptoms persist, intravenously	Hypotension Patient receiving sildenafil or other PDE-5 inhibitor	Topical, oral, or buccal nitrates are acceptable alternatives for patients without ongoing or refractory symptoms 5–10 µg/min by continuous infusion titrated up to 75–100 µg/min until relief of symptoms or limiting side effects (headache or hypotension with a systolic blood pressure <90 mmHg or more than 30% below starting mean arterial pressure levels if significant hypertension is present)
Beta blockers ^b	Unstable angina	PR interval (ECG) <0.24 s 2° or 3° atrioventricular block Heart rate <60 beats/min Systolic pressure <90 mmHg Shock Left ventricular failure Severe reactive airway disease	Metoprolol 25–50 mg by mouth every 6 h If needed, and no heart failure, 5-mg increments by slow (over 1–2 min) IV administration
Calcium channel blockers	Patients whose symptoms are not relieved by adequate doses of nitrates and beta blockers, or in patients unable to tolerate adequate doses of one or both of these agents, or in patients with variant angina	Pulmonary edema Evidence of left ventricular dysfunction (for diltiazem or verapamil)	Dependent on specific agent
Morphine sulfate	Patients whose symptoms are not relieved after three serial sublingual nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy	Hypotension Respiratory depression Confusion Obtundation	2–5 mg IV dose May be repeated every 5–30 min as needed to relieve symptoms and maintain patient comfort

^aAllergy or prior intolerance is a contraindication for all categories of drugs listed in this chart.

^bChoice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance due to existing pulmonary disease, especially asthma, left ventricular dysfunction, risk of hypotension, or severe bradycardia, initial selection should favor a short-acting agent, such as propranolol or metoprolol or the ultra-short-acting agent esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (e.g., 2.5 mg IV metoprolol, 12.5 mg oral metoprolol, or 25 µg/kg per min esmolol as initial doses) rather than complete avoidance of beta blocker therapy.

Note: Some of the recommendations in this guide suggest the use of agents for purposes or in doses other than those specified by the U.S. Food and Drug Administration. Such recommendations are made after consideration of concerns regarding nonapproved indications. Where made, such recommendations are based on more recent clinical trials or expert consensus. 2°, second-degree; 3°, third-degree; ECG, electrocardiogram; IV, intravenous.

Source: Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.

Continued benefit of treatment with the combination of aspirin and clopidogrel has been observed both in patients treated conservatively and in those who underwent PCI. This regimen should continue for at least 1 year in patients with NSTEMI-ACS, especially those with a drug-eluting stent, to prevent stent thrombosis. Up to one-third of patients have

an inadequate response to clopidogrel, and a substantial proportion of these cases are related to a genetic variant of the cytochrome P450 system. A variant of the 2C19 gene leads to reduced conversion of clopidogrel into its active metabolite, which, in turn, reduces platelet inhibition and is associated with increases in the incidence of adverse cardiovascular

TABLE 40-2
CLINICAL USE OF ANTITHROMBOTIC THERAPY

Oral Antiplatelet Therapy	
Aspirin	Initial dose of 325 mg nonenteric formulation followed by 75–100 mg/d of an enteric or a nonenteric formulation
Clopidogrel	Loading dose of 300–600 mg followed by 75 mg/d
Prasugrel	Pre-PCI: Loading dose 60 mg followed by 10 mg/d
Ticagrelor	Loading dose of 180 mg followed by 90 mg twice daily
Intravenous Antiplatelet Therapy	
Abciximab	0.25 mg/kg bolus followed by infusion of 0.125 µg/kg per min (maximum 10 µg/min) for 12–24 h
Eptifibatide	180 µg/kg bolus followed 10 min later by second bolus of 180 µg with infusion of 2.0 µg/kg per min for 72–96 h following first bolus
Tirofiban	25 µg/kg per min followed by infusion of 0.15 µg/kg per min for 48–96 h
Heparins ^a	
Unfractionated heparin (UFH)	^b Bolus 70–100 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U/kg per h (initial maximum 1000 U/h) titrated to ACT 250–300 s
Enoxaparin	1 mg/kg SC every 12 h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg once daily if creatine clearance <30 cc/min
Fondaparinux	2.5 mg SC qd
Bivalirudin	Initial IV bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg per h.

^aOther low-molecular-weight heparins exist beyond those listed.
^bIf no glycoprotein IIb/IIIa inhibitor planned.
Abbreviations: ACT, activated clotting time for HemoTec; IV, intravenous; SC, subcutaneously.
Source: Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.

events. Alternate P2Y₁₂ blockers, such as prasugrel or ticagrelor (see below) used with aspirin, should be considered in patients with NSTEMI-ACS who develop a coronary event while receiving clopidogrel and aspirin or who are hyporesponsive to clopidogrel as identified by platelet and/or genetic testing, although such testing is not yet widespread.

A second P2Y₁₂ blocker, prasugrel, also a thienopyridine, achieves a more rapid onset and higher level of platelet inhibition than clopidogrel. It has been approved for ACS patients following angiography in whom PCI is planned. It should be administered at a loading dose of 60 mg followed by 10 mg/d for up to 15 months. The TRITON-TIMI 38 trial showed that relative to clopidogrel, prasugrel reduced the risk of cardiovascular death, MI, or stroke significantly, albeit with an increase in major bleeding. Stent thrombosis was reduced by half. This agent is contraindicated in patients with prior stroke or transient ischemic attack or at high risk for bleeding. It has not been found to be effective in patients treated by a conservative strategy (see below).

Ticagrelor is a novel, potent, reversible platelet P2Y₁₂ inhibitor. It has been shown in the PLATO trial to reduce the risk of cardiovascular death, MI, or stroke compared with clopidogrel in ACS patients who are treated by either an invasive or a conservative strategy. This agent reduced mortality but increased the risk of bleeding not associated with coronary artery bypass grafting. After a loading dose of 180 mg, 90 mg bid is administered as maintenance.

Prior to the development of the oral P2Y₁₂ receptor blockers, many trials had shown the benefit of intravenous glycoprotein IIb/IIIa inhibitors. Their benefit, however, has been small (i.e., only a 10% reduction in death or MI, with a significant increase in major bleeding). Two recent studies failed to show a benefit of routine early initiation of a drug in this class compared with their use only in patients who undergo PCI. The addition of these agents to aspirin and a P2Y₁₂ inhibitor (i.e., triple antiplatelet therapy) should be reserved for unstable patients with recurrent rest pain, elevated cTn, and ECG changes, as well as those who have a coronary thrombus evident on angiography when they undergo PCI.

Anticoagulants Four options are available for anticoagulant therapy to be added to antiplatelet agents: (1) unfractionated heparin (UFH), long the mainstay of therapy; (2) the low-molecular-weight heparin (LMWH), enoxaparin, which has been shown to be superior to UFH in reducing recurrent cardiac events, especially in patients managed by a conservative strategy but with some increase in bleeding; (3) bivalirudin, a direct thrombin inhibitor that is similar in efficacy to either UFH or LMWH but causes less bleeding and is used just prior to and/or during PCI; and (4) the indirect factor Xa inhibitor, fondaparinux, which is equivalent in efficacy to enoxaparin but appears to have a lower risk of major bleeding.

Excessive bleeding is the most important adverse effect of all antithrombotic agents, including both antiplatelet agents and anticoagulants. Therefore, attention must be directed to the doses of antithrombotic agents, accounting for body weight, creatinine clearance, and a previous history of excessive bleeding, as a means of reducing the risk of bleeding. Patients who have experienced a stroke are at higher risk of intracranial bleeding with potent antiplatelet agents and combinations of antithrombotic drugs.

INVASIVE VERSUS CONSERVATIVE STRATEGY Multiple clinical trials have demonstrated the benefit of an early invasive strategy in high-risk patients (i.e., patients with multiple clinical risk factors, ST-segment deviation, and/or positive biomarkers) (**Table 40-3**). In this strategy, following treatment with anti-ischemic and antithrombotic agents, coronary arteriography is carried out within $\leq$ 48 h of presentation, followed by coronary revascularization (PCI or coronary artery bypass grafting), depending on the coronary anatomy. In low-risk patients, the outcomes from an invasive strategy are similar to those obtained from a conservative strategy. The latter consists of anti-ischemic and antithrombotic therapy followed by “watchful waiting,” in which the patient is closely observed and coronary arteriography is carried out only if rest pain or ST-segment changes recur, a biomarker of necrosis becomes positive, or there is evidence of severe ischemia on a stress test.

LONG-TERM MANAGEMENT

The time of hospital discharge is a “teachable moment” for the patient with NSTEMI-ACS, when the physician can review and optimize the medical regimen. Risk-factor modification is key, and the caregiver should discuss with the patient the importance of smoking cessation, achieving optimal weight, daily exercise, blood-pressure control, following an appropriate diet, control of hyperglycemia (in diabetic patients), and lipid management as recommended for patients with chronic stable angina (**Chap. 39**).

There is evidence of benefit with long-term therapy with five classes of drugs that are directed at different components of the atherothrombotic process. Beta blockers, statins (at a high dose, e.g., atorvastatin 80 mg/d), and ACE inhibitors or angiotensin receptor blockers are recommended for long-term plaque stabilization. Antiplatelet therapy, now recommended to be the combination of low-dose (75–100 mg/d) aspirin and a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) for 1 year, with aspirin continued thereafter, prevents or reduces the severity of any thrombosis that would occur if a plaque were to rupture.

Registries have shown that women and racial minorities, as well as patients with NSTEMI-ACS at high risk, including the elderly and patients with diabetes or chronic kidney disease, are less likely to receive evidence-based pharmacologic and interventional therapies with resultant poorer clinical outcomes and quality of life. Special attention should be directed to these groups.

PRINZMETAL’S VARIANT ANGINA

In 1959 Prinzmetal et al. described a syndrome of severe ischemic pain that usually occurs at rest and is associated with transient ST-segment elevation. Prinzmetal’s variant angina (PVA) is caused by focal spasm of an epicardial coronary artery, leading to severe transient myocardial

TABLE 40-3

CLASS I RECOMMENDATIONS FOR USE OF AN EARLY INVASIVE STRATEGY IN PATIENTS WITH NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME ^a
CLASS I (LEVEL OF EVIDENCE: A) INDICATIONS
Recurrent angina at rest/low-level activity despite treatment
Elevated TnT or TnI
New ST-segment depression
CHF symptoms, rales, MR EF <0.40
Sustained VT PCI <6 months, prior CABG
High-risk findings from noninvasive testing
Hemodynamic instability
Mild-to-moderate renal dysfunction
Diabetes mellitus
High TIMI Risk Score (>3) ^b

^aAny one of the high-risk indicators.
^bSee Antman (JAMA 284:835, 2000).
Abbreviations: CABG, coronary artery bypass grafting; CHF, congestive heart failure; EF, ejection fraction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; TnI, troponin I; TnT, troponin T; VT, ventricular tachycardia.
Source: Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.

ischemia and occasionally infarction. The cause of the spasm is not well defined, but it may be related to hypercontractility of vascular smooth muscle due to adrenergic vasoconstrictors, leukotrienes, or serotonin. For reasons that are not clear, the prevalence of PVA has decreased substantially during the past few decades.

Clinical and angiographic manifestations

Patients with PVA are generally younger and have fewer coronary risk factors (with the exception of cigarette smoking) than do patients with NSTEMI-ACS. Cardiac examination is usually unremarkable in the absence of ischemia. The clinical diagnosis of PVA is made by the detection of transient ST-segment elevation with rest pain. Many patients also exhibit multiple episodes of asymptomatic ST-segment elevation (silent ischemia). Small elevations of troponin may occur in patients with prolonged attacks.

Coronary angiography demonstrates transient coronary spasm as the diagnostic hallmark of PVA. Atherosclerotic plaques in at least one proximal coronary artery occur in about half of patients, and in these patients, spasm usually occurs within 1 cm of the plaque. Focal spasm is most common in the right coronary artery, and it may occur at one or more sites in one artery or in multiple arteries simultaneously.

468 Hyperventilation or intracoronary acetylcholine has been used to provoke focal coronary stenosis on angiography or to provoke rest angina with ST-segment elevation to establish the diagnosis.

TREATMENT Prinzmetal's Variant Angina

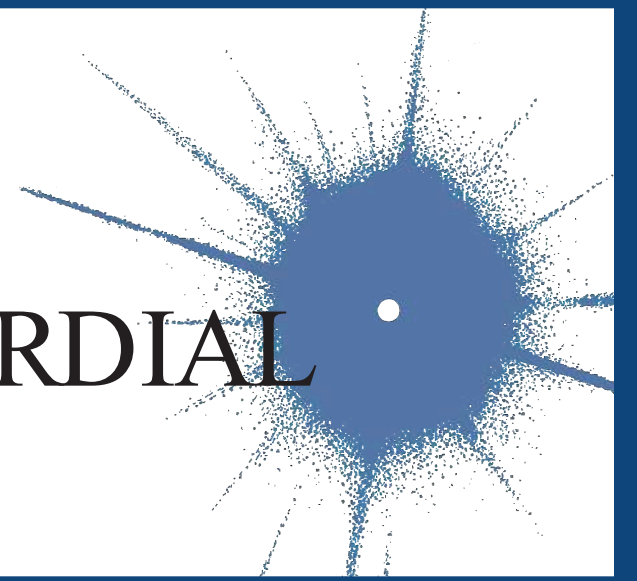
Nitrates and calcium channel blockers are the main therapeutic agents. Aspirin may actually increase the severity of ischemic episodes, possibly as a result of the sensitivity of coronary tone to modest changes in the synthesis of prostacyclin. The response to beta blockers is variable. Coronary revascularization may be helpful in patients who also have discrete, flow-limiting, proximal fixed obstructive lesions.

Prognosis

Many patients with PVA pass through an acute, active phase, with frequent episodes of angina and cardiac events during the first 6 months after presentation. Survival at 5 years is excellent (□90–95%). Patients with no or mild fixed coronary obstruction tend to experience a more benign course than do patients with associated severe obstructive lesions. Nonfatal MI occurs in up to 20% of patients by 5 years. Patients with PVA who develop serious arrhythmias during spontaneous episodes of pain are at a higher risk for sudden cardiac death. In most patients who survive an infarction or the initial 3- to 6-month period of frequent episodes, there is a tendency for symptoms and cardiac events to diminish over time.

CHAPTER 41

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION



Elliott M. Antman ■ Joseph Loscalzo

Acute myocardial infarction (AMI) is one of the most common diagnoses in hospitalized patients in industrialized countries. In the United States, approximately 525,000 patients experience a new AMI, and 190,000 experience a recurrent AMI each year. More than half of AMI-related deaths occur before the stricken individual reaches the hospital. The in-hospital mortality rate after admission for AMI has declined from 10% to about 6% over the past decade. The 1-year mortality rate after AMI is about 15%. Mortality is approximately fourfold higher in elderly patients (over age 75) as compared with younger patients.

When patients with prolonged ischemic discomfort at rest are first seen, the working clinical diagnosis is that they are suffering from an acute coronary syndrome (**Fig. 41-1**). The 12-lead electrocardiogram (ECG) is a pivotal diagnostic and triage tool because it is at the center of the decision pathway for management; it permits distinction of those patients presenting with ST-segment elevation from those presenting without ST-segment elevation. Serum cardiac biomarkers are obtained to distinguish unstable angina (UA) from non-ST-segment elevation myocardial infarction (NSTEMI) and to assess the magnitude of an ST-segment elevation myocardial infarction (STEMI). This chapter focuses on the evaluation and management of patients with STEMI, while **Chap. 40** discusses UA/NSTEMI.

PATHOPHYSIOLOGY: ROLE OF ACUTE PLAQUE RUPTURE

STEMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis. Slowly developing, high-grade coronary artery stenoses do not typically precipitate STEMI because

of the development of a rich collateral network over time. Instead, STEMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury. This injury is produced or facilitated by factors such as cigarette smoking, hypertension, and lipid accumulation. In most cases, STEMI occurs when the surface of an atherosclerotic plaque becomes disrupted (exposing its contents to the blood) and conditions (local or systemic) favor thrombogenesis. A mural thrombus forms at the site of plaque disruption, and the involved coronary artery becomes occluded. Histologic studies indicate that the coronary plaques prone to disruption are those with a rich lipid core and a thin fibrous cap (**Chap. 36**). After an initial platelet monolayer forms at the site of the disrupted plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, thromboxane A₂ (a potent local vasoconstrictor) is released, further platelet activation occurs, and potential resistance to fibrinolysis develops.

In addition to the generation of thromboxane A₂, activation of platelets by agonists promotes a conformational change in the glycoprotein IIb/IIIa receptor. Once converted to its functional state, this receptor develops a high affinity for soluble adhesive proteins (i.e., integrins) such as fibrinogen. Since fibrinogen is a multivalent molecule, it can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation.

The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the disrupted plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin. Fluid-phase and clot-bound thrombin participates in an autoamplification reaction leading to further activation of the coagulation cascade. The culprit coronary artery

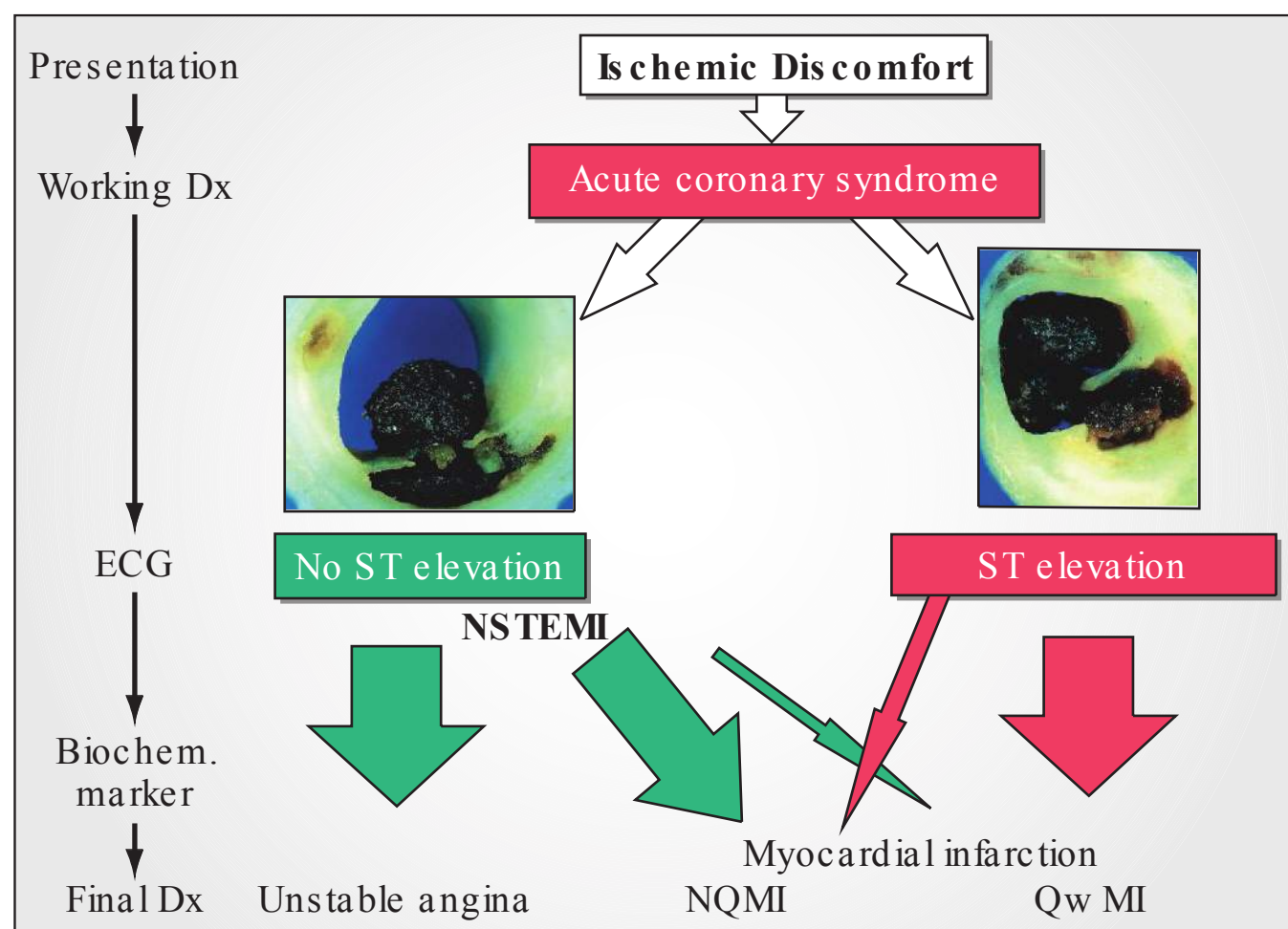


FIGURE 41-1

Acute coronary syndromes. Following disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (right) or subtotally occlusive thrombus (left). Patients with ischemic discomfort may present with or without ST-segment elevation. Of patients with ST-segment elevation, the majority (wide red arrow) ultimately develop a Q wave on the ECG (Qw MI), while a minority (thin red arrow) do not develop Q wave and, in older literature, were said to have sustained a non-Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from either unstable angina or a non-ST-segment elevation MI (NSTEMI) (wide green arrows), a distinction that is ultimately made based on the presence or absence of a serum cardiac marker such as CK-MB or a cardiac troponin detected in the blood. The majority of patients presenting with NSTEMI do not develop a Q wave on the ECG; a minority develop a Qw MI (thin green arrow). Dx, diagnosis; ECG, electrocardiogram; MI, myocardial infarction. (Adapted from CW Hamm et al: *Lancet* 358:1533, 2001, and MJ Davies: *Heart* 83:361, 2000; with permission from the BMJ Publishing Group.)

eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands.

In rare cases, STEMI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic—particularly inflammatory—diseases. The amount of myocardial damage caused by coronary occlusion depends on (1) the territory supplied by the affected vessel, (2) whether or not the vessel becomes totally occluded, (3) the duration of coronary occlusion, (4) the quantity of blood supplied by collateral vessels to the affected tissue, (5) the demand for oxygen of the myocardium whose blood supply has been suddenly limited, (6) endogenous factors that can produce early spontaneous lysis of the occlusive thrombus, and (7) the adequacy of myocardial perfusion in the infarct zone when flow is restored in the occluded epicardial coronary artery.

Patients at increased risk for developing STEMI include those with multiple coronary risk factors (**Chap. 36**) and those with UA (**Chap. 40**). Less common underlying medical conditions predisposing patients to STEMI include hypercoagulability, collagen vascular disease, cocaine abuse, and intracardiac thrombi or masses that can produce coronary emboli.

There have been major advances in the management of STEMI with recognition that the “chain of survival” involves a highly integrated system starting with pre-hospital care and extending to early hospital management so as to provide expeditious implementation of a reperfusion strategy.

CLINICAL PRESENTATION

In up to one-half of cases, a precipitating factor appears to be present before STEMI, such as vigorous physical exercise, emotional stress, or a medical or surgical illness. Although STEMI may commence at any time of the day or night, circadian variations have been reported such that clusters are seen in the morning within a few hours of awakening.

Pain is the most common presenting complaint in patients with STEMI. The pain is deep and visceral; adjectives commonly used to describe it are heavy, squeezing, and crushing, although, occasionally, it is described as stabbing or burning (**Chap. 4**). It is similar in character to the discomfort of angina pectoris (**Chap. 39**) but commonly occurs at rest, is usually more severe, and lasts longer. Typically, the pain involves the central portion of the chest and/or the epigastrium, and, on occasion, it radiates to the arms. Less common sites of radiation include the abdomen, back, lower jaw, and neck. The frequent location of the pain beneath the xiphoid and epigastrium and the patients’ denial that they may be suffering a heart attack are chiefly responsible for the common mistaken impression of indigestion. The pain of STEMI may radiate as high as the occipital area but not below the umbilicus. It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom. The pain may commence when the patient is at rest, but when it begins during a period of exertion, it does not usually subside with cessation of activity, in contrast to angina pectoris.

The pain of STEMI can simulate pain from acute pericarditis (**Chap. 28**), pulmonary embolism (**Chap. 45**), acute aortic dissection (**Chap. 46**), costochondritis, and gastrointestinal disorders. These conditions should therefore be considered in the differential diagnosis. Radiation of discomfort to the trapezius is not seen in patients with STEMI and may be a useful distinguishing feature that suggests pericarditis is the correct diagnosis. However, pain is not uniformly present in

patients with STEMI. The proportion of painless STE-MIs is greater in patients with diabetes mellitus, and it increases with age. In the elderly, STEMI may present as sudden-onset breathlessness, which may progress to pulmonary edema. Other less common presentations, with or without pain, include sudden loss of consciousness, a confusional state, a sensation of profound weakness, the appearance of an arrhythmia, evidence of peripheral embolism, or merely an unexplained drop in arterial pressure.

PHYSICAL FINDINGS

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and coolness of the extremities occurs commonly. The combination of substernal chest pain persisting for >30 min and diaphoresis strongly suggests STEMI. Although many patients have a normal pulse rate and blood pressure within the first hour of STEMI, about one-fourth of patients with anterior infarction have manifestations of sympathetic nervous system hyperactivity (tachycardia and/or hypertension), and up to one-half with inferior infarction show evidence of parasympathetic hyperactivity (bradycardia and/or hypotension).

The precordium is usually quiet, and the apical impulse may be difficult to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infarcted myocardium may develop in the periapical area within the first days of the illness and then may resolve. Other physical signs of ventricular dysfunction include fourth and third heart sounds, decreased intensity of the first heart sound, and paradoxical splitting of the second heart sound (**Chap. 9**). A transient midsystolic or late systolic apical systolic murmur due to dysfunction of the mitral valve apparatus may be present. A pericardial friction rub may be heard in patients with transmural STEMI at some time in the course of the disease, if they are examined frequently. The carotid pulse is often decreased in volume, reflecting reduced stroke volume. Temperature elevations up to 38°C may be observed during the first week after STEMI. The arterial pressure is variable; in most patients with transmural infarction, systolic pressure declines by approximately 10–15 mmHg from the preinfarction state.

LABORATORY FINDINGS

STEMI progresses through the following temporal stages: (1) acute (first few hours–7 days), (2) healing (7–28 days), and (3) healed (≥ 29 days). When

evaluating the results of diagnostic tests for STEMI, the temporal phase of the infarction must be considered. The laboratory tests of value in confirming the diagnosis may be divided into four groups: (1) ECG, (2) serum cardiac biomarkers, (3) cardiac imaging, and (4) non-specific indices of tissue necrosis and inflammation.

ELECTROCARDIOGRAM

The electrocardiographic manifestations of STEMI are described in **Chap. 11**. During the initial stage, total occlusion of an epicardial coronary artery produces ST-segment elevation. Most patients initially presenting with ST-segment elevation ultimately evolve Q waves on the ECG. However, Q waves in the leads overlying the infarct zone may vary in magnitude and even appear only transiently, depending on the reperfusion status of the ischemic myocardium and restoration of transmembrane potentials over time. A small proportion of patients initially presenting with ST-segment elevation will not develop Q waves when the obstructing thrombus is not totally occlusive, obstruction is transient, or if a rich collateral network is present. Among patients presenting with ischemic discomfort but without ST-segment elevation, if a serum cardiac biomarker of necrosis (see below) is detected, the diagnosis of NSTEMI is ultimately made (Fig. 41-1). A minority of patients who present initially without ST-segment elevation may develop a Q-wave MI. Previously, it was believed that transmural myocardial infarction (MI) is present if the ECG demonstrates Q waves or loss of R waves, and non-transmural MI may be present if the ECG shows only transient ST-segment and T-wave changes. However, electrocardiographic-pathologic correlations are far from perfect and terms such as Q-wave MI, non-Q-wave MI, transmural MI, and nontransmural MI, have been replaced by STEMI and NSTEMI (Fig. 41-1). Contemporary studies using magnetic resonance imaging (MRI) suggest that the development of a Q wave on the ECG is more dependent on the volume of infarcted tissue rather than the transmural extent of infarction.

SERUM CARDIAC BIOMARKERS

Certain proteins, called serum cardiac biomarkers, are released from necrotic heart muscle after STEMI. The rate of liberation of specific proteins differs depending on their intracellular location, their molecular weight, and the local blood and lymphatic flow. Cardiac biomarkers become detectable in the peripheral blood once the capacity of the cardiac lymphatics to clear the interstitium of the infarct zone is exceeded and spillover into the venous circulation occurs. The temporal pattern of protein release is of diagnostic importance. The criteria for AMI require a rise and/or fall in cardiac biomarker

values with at least one value above the 99th percentile of the upper reference limit for normal individuals

Cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI) have amino-acid sequences different from those of the skeletal muscle forms of these proteins. These differences permitted the development of quantitative assays for cTnT and cTnI with highly specific monoclonal antibodies. Since cTnT and cTnI are not normally detectable in the blood of healthy individuals but may increase after STEMI to levels many times higher than the upper reference limit (the highest value seen in 99% of a reference population not suffering from MI), the measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI (**Fig. 41-2**). With improvements in the assays for the

cardiac-specific troponins, it is now possible to detect concentrations <1 ng/L in patients without ischemic-type chest discomfort. The cardiac troponins are particularly valuable when there is clinical suspicion of either skeletal muscle injury or a small MI that may be below the detection limit for creatine phosphokinase (CK) and its MB isoenzyme (CK-MB) measurements, and they are, therefore, of particular value in distinguishing UA from NSTEMI. In practical terms, the high-sensitivity troponin assays are of less immediate value in patients with STEMI. Contemporary urgent reperfusion strategies necessitate making a decision (based largely on a combination of clinical and ECG findings) before the results of blood tests have returned from the laboratory. Levels of cTnI and cTnT may remain elevated for 7–10 days after STEMI.

CK rises within 4–8 h and generally returns to normal by 48–72 h (**Fig. 41-2**). An important drawback of total CK measurement is its lack of specificity for STEMI, as CK may be elevated with skeletal muscle disease or trauma, including intramuscular injection. The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentrations in extracardiac tissue and, therefore, is considerably more specific. However, cardiac surgery, myocarditis, and electrical cardioversion often result in elevated serum levels of the MB isoenzyme. A ratio (relative index) of CK-MB mass to CK activity ≥ 2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CK-MB elevation.

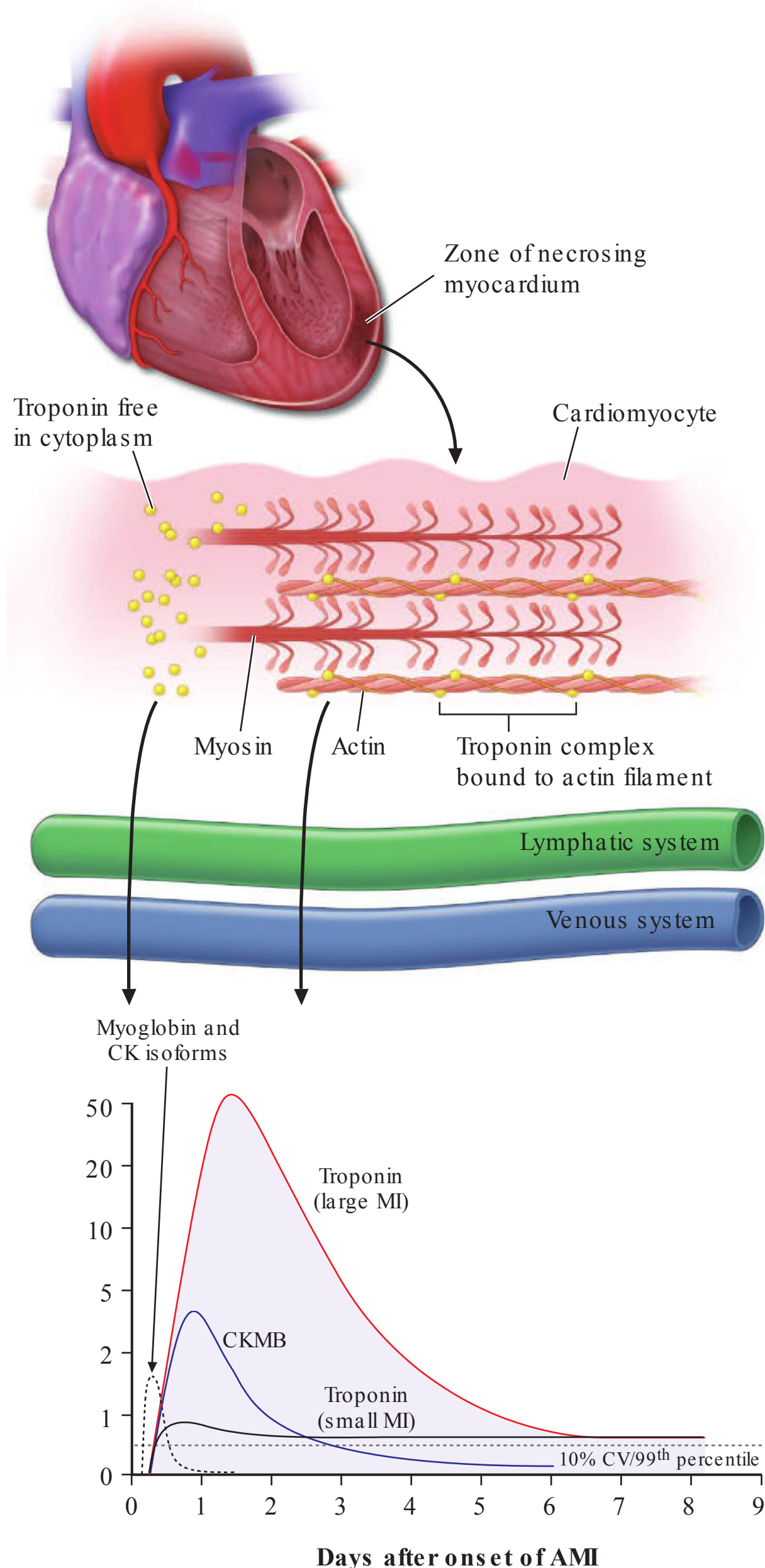


FIGURE 41-2

The zone of necrotizing myocardium is shown at the top of the figure, followed in the middle portion of the figure by a diagram of a cardiomyocyte that is in the process of releasing biomarkers. The biomarkers that are released into the interstitium are first cleared by lymphatics followed subsequently by spillover into the venous system. After disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first (left-most arrow in bottom portion of figure). Markers such as myoglobin and CK isoforms are rapidly released, and blood levels rise quickly above the cutoff limit; this is then followed by a more protracted release of biomarkers from the disintegrating myofilaments that may continue for several days. Cardiac troponin levels rise to about 20 to 50 times the upper reference limit (the 99th percentile of values in a reference control group) in patients who have a “classic” acute myocardial infarction (MI) and sustain sufficient myocardial necrosis to result in abnormally elevated levels of the MB fraction of creatine kinase (CK-MB). Clinicians can now diagnose episodes of microinfarction by sensitive assays that detect cardiac troponin elevations above the upper reference limit, even though CK-MB levels may still be in the normal reference range (not shown). CV, coefficient of variation. (Modified from EM Antman: Decision making with cardiac troponin tests. *N Engl J Med* 346:2079, 2002 and AS Jaffe, LB Abujar, FS Apple: Biomarkers in acute cardiac disease: The present and the future. *J Am Coll Cardiol* 48:1, 2006.)

Many hospitals are using cTnT or cTnI rather than CK-MB as the routine serum cardiac marker for diagnosis of STEMI, although any of these analytes remain clinically acceptable. It is not cost-effective to measure both a cardiac-specific troponin and CK-MB at all time points in every patient.

While it has long been recognized that the total quantity of protein released correlates with the size of the infarct, the peak protein concentration correlates only weakly with infarct size. Recanalization of a coronary artery occlusion (either spontaneously or by mechanical or pharmacologic means) in the early hours of STEMI causes earlier peaking of biomarker measurements (Fig. 41-2) because of a rapid washout from the interstitium of the infarct zone, quickly overwhelming lymphatic clearance of the proteins.

The nonspecific reaction to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain and persists for 3–7 days; the white blood cell count often reaches levels of 12,000–15,000/ μ L. The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks.

CARDIAC IMAGING

Abnormalities of wall motion on two-dimensional echocardiography (**Chap. 12**) are almost universally present. Although acute STEMI cannot be distinguished from an old myocardial scar or from acute severe ischemia by echocardiography, the ease and safety of the procedure make its use appealing as a screening tool in the Emergency Department setting. When the ECG is not diagnostic of STEMI, early detection of the presence or absence of wall motion abnormalities by echocardiography can aid in management decisions, such as whether the patient should receive reperfusion therapy (e.g., fibrinolysis or a percutaneous coronary intervention [PCI]). Echocardiographic estimation of left ventricular (LV) function is useful prognostically; detection of reduced function serves as an indication for therapy with an inhibitor of the renin-angiotensin-aldosterone system. Echocardiography may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of STEMI.

Several radionuclide imaging techniques (**Chap. 12**) are available for evaluating patients with suspected STEMI. However, these imaging modalities are used less often than echocardiography because they are more cumbersome and lack sensitivity and specificity

in many clinical circumstances. Myocardial perfusion imaging with [^{201}Tl] or [$^{99\text{m}}\text{Tc}$]-sestamibi, which are distributed in proportion to myocardial blood flow and concentrated by viable myocardium (**Chap. 39**), reveals a defect (“cold spot”) in most patients during the first few hours after development of a transmural infarct. Although perfusion scanning is extremely sensitive, it cannot distinguish acute infarcts from chronic scars and, thus, is not specific for the diagnosis of acute MI. Radionuclide ventriculography, carried out with [$^{99\text{m}}\text{Tc}$]-labeled red blood cells, frequently demonstrates wall motion disorders and reduction in the ventricular ejection fraction in patients with STEMI. While of value in assessing the hemodynamic consequences of infarction and in aiding in the diagnosis of RV infarction when the RV ejection fraction is depressed, this technique is nonspecific, as many cardiac abnormalities other than MI alter the radionuclide ventriculogram.

MI can be detected accurately with high-resolution cardiac MRI (**Chap. 12**) using a technique referred to as late enhancement. A standard imaging agent (gadolinium) is administered and images are obtained after a 10-min delay. Since little gadolinium enters normal myocardium, where there are tightly packed myocytes, but does percolate into the expanded intercellular region of the infarct zone, there is a bright signal in areas of infarction that appears in stark contrast to the dark areas of normal myocardium.

An Expert Consensus Task Force for the Universal Definition of Myocardial Infarction has provided a comprehensive set of criteria for the definition of MI that integrates the clinical and laboratory findings discussed earlier (**Table 41-1**) as well as a classification of MI into five types that reflect the clinical circumstances in which it may occur (**Table 41-2**).

INITIAL MANAGEMENT

PREHOSPITAL CARE

The prognosis in STEMI is largely related to the occurrence of two general classes of complications: (1) electrical complications (arrhythmias) and (2) mechanical complications (“pump failure”). Most out-of-hospital deaths from STEMI are due to the sudden development of ventricular fibrillation. The vast majority of deaths due to ventricular fibrillation occur within the first 24 h of the onset of symptoms, and of these, over half occur in the first hour. Therefore, the major elements of prehospital care of patients with suspected STEMI include (1) recognition of symptoms by the patient and prompt seeking of medical attention; (2) rapid deployment of an emergency medical team capable of performing resuscitative maneuvers, including defibrillation; (3) expeditious transportation of the patient to a hospital

TABLE 41-1

DEFINITION OF MYOCARDIAL INFARCTION
Criteria for Acute Myocardial Infarction
The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI: • Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: • Symptoms of ischemia • New or presumed new significant ST-segment T-wave (ST-T) changes or new left bundle branch block (LBBB) • Development of pathologic Q waves in the electrocardiogram (ECG) • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Identification of an intracoronary thrombus by angiography or autopsy • Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes of new LBBB, but death occurred before cardiac biomarkers were obtained or before cardiac biomarker values would be increased. • Percutaneous coronary intervention (PCI)–related MI is arbitrarily defined by elevation of cTn values ($>5 \times$ 99th percentile URL) in patients with normal baseline values ($\leq$99th percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes, or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. • Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. • Coronary artery bypass grafting (CABG)–related MI is arbitrarily defined by elevation of cardiac biomarker values ($>10 \times$ 99th percentile URL) in patients with normal baseline cTn values ($\leq$99th percentile URL). In addition, either (i) new pathologic Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Criteria for Prior Myocardial Infarction
Any one of the following criteria meets the diagnosis for prior MI: • Pathologic Q waves with or without symptoms in the absence of nonischemic causes. • Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause. • Pathologic findings of a prior MI.

Source: KThygesen: Eur Heart J 33:2551, 2012.

TABLE 41-2

CLASSIFICATION OF MYOCARDIAL INFARCTION
Type I: Spontaneous Myocardial Infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD) but on occasion nonobstructive or no CAD.
Type 2: Myocardial Infarction Secondary to an Ischemic Imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy.
Type 3: Myocardial Infarction Resulting in Death When Biomarker Values Are Unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic electrocardiogram (ECG) changes or new left bundle branch block (LBBB), but death occurring before blood samples could be obtained or before cardiac biomarker could rise, or in rare cases, cardiac biomarkers were not collected.
Type 4a: Myocardial Infarction Related to Percutaneous Coronary Intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cardiac troponin (cTn) values $>5 \times$ 99th percentile upper reference limit (URL) in patients with normal baseline values ($\leq$99th percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.
Type 4b: Myocardial Infarction Related to Stent Thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
Type 5: Myocardial Infarction Related to Coronary Artery Bypass Grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values $>10 \times$ 99th percentile URL in patients with normal baseline cTn values ($\leq$99th percentile URL). In addition, either (i) new pathologic Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Source: KThygesen: Eur Heart J 33:2551, 2012.

MANAGEMENT IN THE EMERGENCY DEPARTMENT

facility that is continuously staffed by physicians and nurses skilled in managing arrhythmias and providing advanced cardiac life support; and (4) expeditious implementation of reperfusion therapy (**Fig. 41-3**). The greatest delay usually occurs not during transportation to the hospital but, rather, between the onset of pain and the patient's decision to call for help. This delay can best be reduced by health care professionals educating the public concerning the significance of chest discomfort and the importance of seeking early medical attention. Regular office visits with patients having a history of or who are at risk for ischemic heart disease are important "teachable moments" for clinicians to review the symptoms of STEMI and the appropriate action plan.

Increasingly, monitoring and treatment are carried out by trained personnel in the ambulance, further shortening the time between the onset of the infarction and appropriate treatment. General guidelines for initiation of fibrinolysis in the prehospital setting include the ability to transmit 12-lead ECGs to confirm the diagnosis, the presence of paramedics in the ambulance, training of paramedics in the interpretation of ECGs and management of STEMI, and online medical command and control that can authorize the initiation of treatment in the field.

In the Emergency Department, the goals for the management of patients with suspected STEMI include control of cardiac discomfort, rapid identification of patients who are candidates for urgent reperfusion therapy, triage of lower-risk patients to the appropriate location in the hospital, and avoidance of inappropriate discharge of patients with STEMI. Many aspects of the treatment of STEMI are initiated in the Emergency Department and then continued during the in-hospital phase of management (**Fig. 41-4**). The overarching goal is to minimize the time from first medical contact to initiation of reperfusion therapy. This may involve transfer from a non-PCI hospital to one that is PCI capable, with a goal of initiating PCI within 120 min of first medical contact (**Fig. 41-4**).

Aspirin is essential in the management of patients with suspected STEMI and is effective across the entire spectrum of acute coronary syndromes (**Fig. 41-1**). Rapid inhibition of cyclooxygenase-1 in platelets followed by a reduction of thromboxane A₂ levels is achieved by buccal absorption of a chewed 160–325-mg tablet in the Emergency Department. This measure

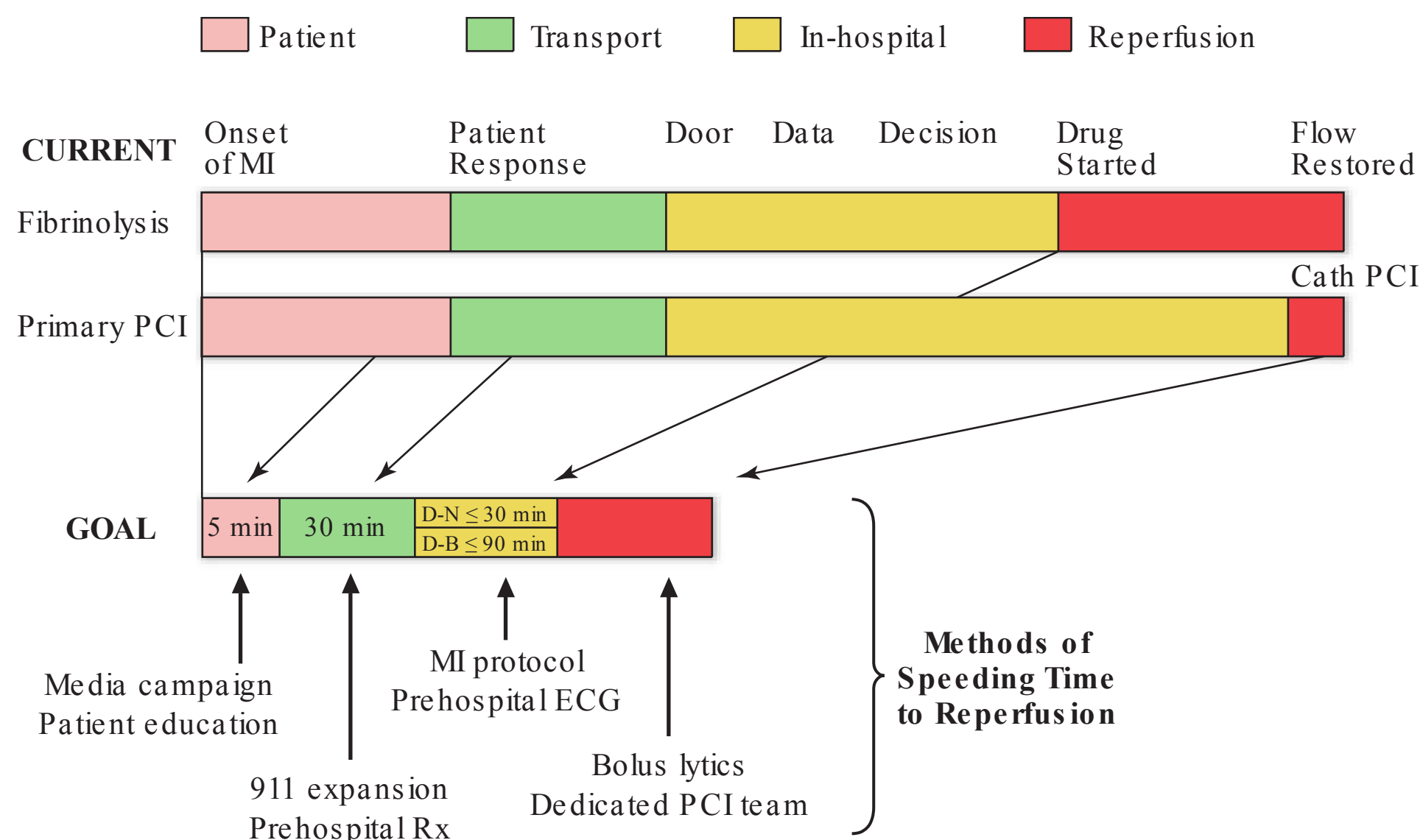


FIGURE 41-3

Major components of time delay between onset of symptoms from ST-segment elevation myocardial infarction and restoration of flow in the infarct-related artery. Plotted sequentially from left to right are the times for patients to recognize symptoms and seek medical attention, transportation to the hospital, in-hospital decision making, implementation of reperfusion strategy, and restoration of flow once the reperfusion strategy has been initiated. The time to initiate fibrinolytic therapy is the "door-to-needle" (D-N) time; this is followed by the period of

time required for pharmacologic restoration of flow. More time is required to move the patient to the catheterization laboratory for a percutaneous coronary interventional (PCI) procedure, referred to as the "door-to-balloon" (D-B) time, but restoration of flow in the epicardial infarct-related artery occurs promptly after PCI. At the bottom is a variety of methods for speeding the time to reperfusion along with the goals for the time intervals for the various components of the time delay. (Adapted from CP Cannon et al: *J Thromb Thrombol* 1:27, 1994.)

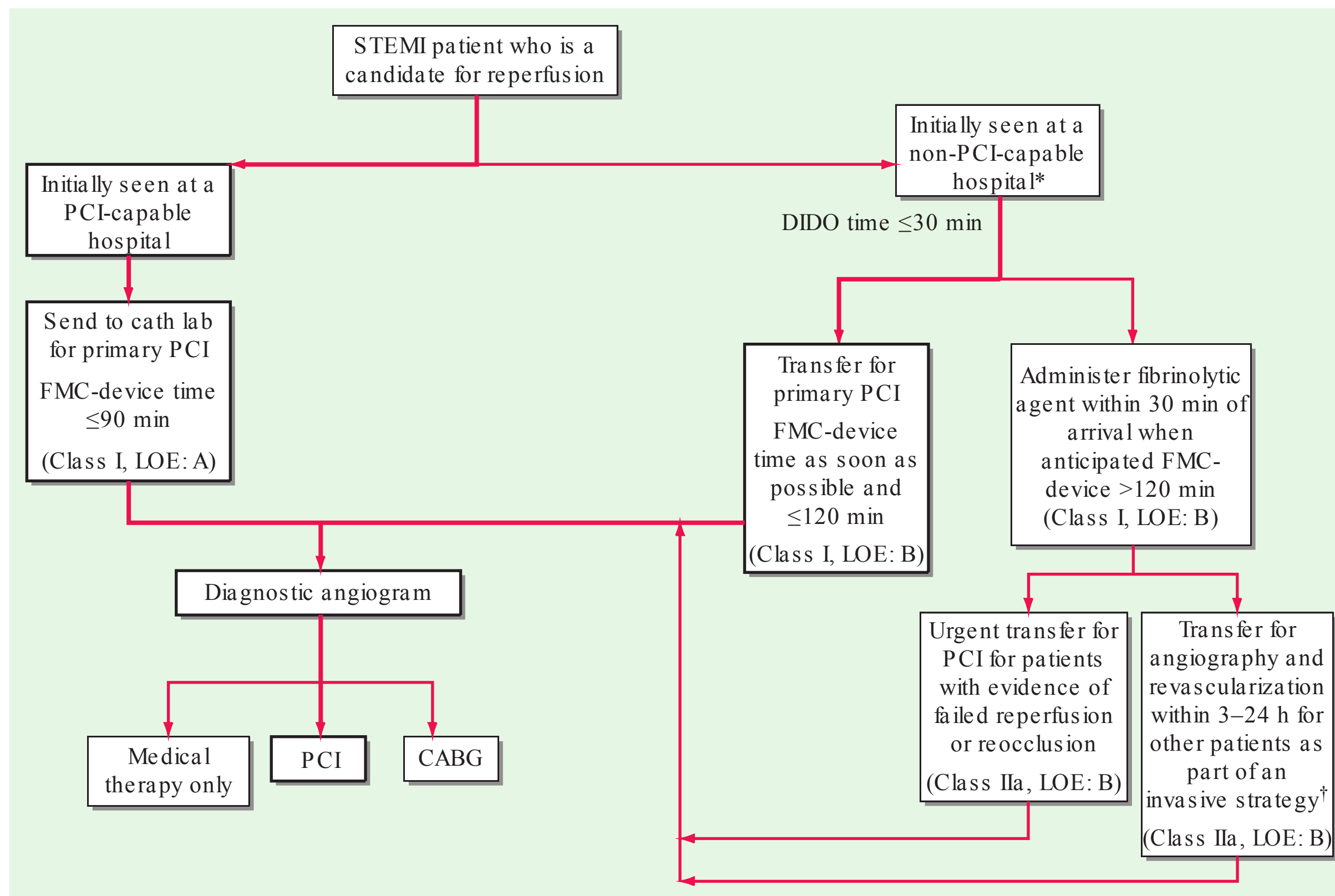


FIGURE 41-4

Reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI). The bold arrows and boxes are the preferred strategies. Performance of percutaneous coronary intervention (PCI) is dictated by an anatomically appropriate culprit stenosis. *Patients with cardiogenic shock or severe heart failure initially seen at a non-PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as

possible, irrespective of time delay from myocardial infarction (MI) onset (Class I, LOE: B). †Angiography and revascularization should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. CABG, coronary artery bypass graft; DIDO, door-in–door-out; FMC, first medical contact; LOE, level of evidence; STEMI, ST-elevation myocardial infarction. (Adapted with permission from P O’Gara et al: *Circulation* 127:e362, 2013.)

should be followed by daily oral administration of aspirin in a dose of 75–162 mg.

In patients whose arterial O₂ saturation is normal, supplemental O₂ is of limited if any clinical benefit and therefore is not cost-effective. However, when hypoxemia is present, O₂ should be administered by nasal prongs or face mask (2–4 L/min) for the first 6–12 h after infarction; the patient should then be reassessed to determine if there is a continued need for such treatment.

CONTROL OF DISCOMFORT

Sublingual nitroglycerin can be given safely to most patients with STEMI. Up to three doses of 0.4 mg should be administered at about 5-min intervals. In addition to diminishing or abolishing chest discomfort, nitroglycerin may be capable of both decreasing myocardial oxygen demand (by lowering preload) and increasing myocardial oxygen supply (by dilating infarct-related coronary vessels or collateral vessels).

In patients whose initially favorable response to sublingual nitroglycerin is followed by the return of chest discomfort, particularly if accompanied by other evidence of ongoing ischemia such as further ST-segment or T-wave shifts, the use of intravenous nitroglycerin should be considered. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (<90 mmHg) or in whom there is clinical suspicion of RV infarction (inferior infarction on ECG, elevated jugular venous pressure, clear lungs, and hypotension). Nitrates should not be administered to patients who have taken a phosphodiesterase-5 inhibitor for erectile dysfunction within the preceding 24 h, because it may potentiate the hypotensive effects of nitrates. An idiosyncratic reaction to nitrates, consisting of sudden marked hypotension, sometimes occurs but can usually be reversed promptly by the rapid administration of intravenous atropine.

Morphine is a very effective analgesic for the pain associated with STEMI. However, it may reduce sympathetically mediated arteriolar and venous constriction,

and the resulting venous pooling may reduce cardiac output and arterial pressure. These hemodynamic disturbances usually respond promptly to elevation of the legs, but in some patients, volume expansion with intravenous saline is required. The patient may experience diaphoresis and nausea, but these events usually pass and are replaced by a feeling of well-being associated with the relief of pain. Morphine also has a vagotonic effect and may cause bradycardia or advanced degrees of heart block, particularly in patients with inferior infarction. These side effects usually respond to atropine (0.5 mg intravenously). Morphine is routinely administered by repetitive (every 5 min) intravenous injection of small doses (2–4 mg), rather than by the subcutaneous administration of a larger quantity, because absorption may be unpredictable by the latter route.

Intravenous beta blockers are also useful in the control of the pain of STEMI. These drugs control pain effectively in some patients, presumably by diminishing myocardial O_2 demand and hence ischemia. More important, there is evidence that intravenous beta blockers reduce the risks of reinfarction and ventricular fibrillation (see “Beta-Adrenoceptor Blockers” below). However, patient selection is important when considering beta blockers for STEMI. Oral beta blocker therapy should be initiated in the first 24 h for patients who do not have any of the following: (1) signs of heart failure, (2) evidence of a low-output state, (3) increased risk for cardiogenic shock, or (4) other relative contraindications to beta blockade (PR interval greater than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease). A commonly employed regimen is metoprolol, 5 mg every 2–5 min for a total of three doses, provided the patient has a heart rate >60 beats/min, systolic pressure >100 mmHg, a PR interval <0.24 s, and rales that are no higher than 10 cm up from the diaphragm. Fifteen minutes after the last intravenous dose, an oral regimen is initiated of 50 mg every 6 h for 48 h, followed by 100 mg every 12 h.

Unlike beta blockers, calcium antagonists are of little value in the acute setting, and there is evidence that short-acting dihydropyridines may be associated with an increased mortality risk.

MANAGEMENT STRATEGIES

The primary tool for screening patients and making triage decisions is the initial 12-lead ECG. When ST-segment elevation of at least 2 mm in two contiguous precordial leads and 1 mm in two adjacent limb leads is present, a patient should be considered a candidate for reperfusion therapy (Fig. 41-4). The process of selecting patients for fibrinolysis versus primary PCI (angioplasty or stenting; **Chap. 42**) is discussed below. In the

absence of ST-segment elevation, fibrinolysis is not helpful, and evidence exists suggesting that it may be harmful.

LIMITATION OF INFARCT SIZE

The quantity of myocardium that becomes necrotic as a consequence of a coronary artery occlusion is determined by factors other than just the site of occlusion. While the central zone of the infarct contains necrotic tissue that is irretrievably lost, the fate of the surrounding ischemic myocardium (ischemic penumbra) may be improved by timely restoration of coronary perfusion, reduction of myocardial O_2 demands, prevention of the accumulation of noxious metabolites, and blunting of the impact of mediators of reperfusion injury (e.g., calcium overload and oxygen-derived free radicals). Up to one-third of patients with STEMI may achieve spontaneous reperfusion of the infarct-related coronary artery within 24 h and experience improved healing of infarcted tissue. Reperfusion, either pharmacologically (by fibrinolysis) or by PCI, accelerates the opening of infarct-related arteries in those patients in whom spontaneous fibrinolysis ultimately would have occurred and also greatly increases the number of patients in whom restoration of flow in the infarct-related artery is accomplished. Timely restoration of flow in the epicardial infarct-related artery combined with improved perfusion of the downstream zone of infarcted myocardium results in a limitation of infarct size. Protection of the ischemic myocardium by the maintenance of an optimal balance between myocardial O_2 supply and demand through pain control, treatment of congestive heart failure (CHF), and minimization of tachycardia and hypertension extends the “window” of time for the salvage of myocardium by reperfusion strategies.

Glucocorticoids and nonsteroidal anti-inflammatory agents, with the exception of aspirin, should be avoided in patients with STEMI. They can impair infarct healing and increase the risk of myocardial rupture, and their use may result in a larger infarct scar. In addition, they can increase coronary vascular resistance, thereby potentially reducing flow to ischemic myocardium.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

(See also **Chap. 42**) PCI, usually angioplasty and/or stenting without preceding fibrinolysis, referred to as primary PCI, is effective in restoring perfusion in STEMI when carried out on an emergency basis in the first few hours of MI. It has the advantage of being applicable to patients who have contraindications to fibrinolytic therapy (see below) but otherwise are

considered appropriate candidates for reperfusion. It appears to be more effective than fibrinolysis in opening occluded coronary arteries and, when performed by experienced operators in dedicated medical centers, is associated with better short-term and long-term clinical outcomes. Compared with fibrinolysis, primary PCI is generally preferred when the diagnosis is in doubt, cardiogenic shock is present, bleeding risk is increased, or symptoms have been present for at least 2–3 h when the clot is more mature and less easily lysed by fibrinolytic drugs. However, PCI is expensive in terms of personnel and facilities, and its applicability is limited by its availability, around the clock, in only a minority of hospitals (Fig. 41-4).

FIBRINOLYSIS

If no contraindications are present (see below), fibrinolytic therapy should ideally be initiated within 30 min of presentation (i.e., door-to-needle time ≤ 30 min). The principal goal of fibrinolysis is prompt restoration of full coronary arterial patency. The fibrinolytic agents tissue plasminogen activator (tPA), streptokinase, tenecteplase (TNK), and reteplase (rPA) have been approved by the U.S. Food and Drug Administration for intravenous use in patients with STEMI. These drugs all act by promoting the conversion of plasminogen to plasmin, which subsequently lyses fibrin thrombi. Although considerable emphasis was first placed on a distinction between more fibrin-specific agents, such as tPA, and non-fibrin-specific agents, such as streptokinase, it is now recognized that these differences are only relative, as some degree of systemic fibrinolysis occurs with the former agents. TNK and rPA are referred to as bolus fibrinolytics since their administration does not require a prolonged intravenous infusion.

When assessed angiographically, flow in the culprit coronary artery is described by a simple qualitative scale called the Thrombolysis in Myocardial Infarction (TIMI) grading system: grade 0 indicates complete occlusion of the infarct-related artery; grade 1 indicates some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary bed; grade 2 indicates perfusion of the entire infarct vessel into the distal bed, but with flow that is delayed compared with that of a normal artery; and grade 3 indicates full perfusion of the infarct vessel with normal flow. The latter is the goal of reperfusion therapy, because full perfusion of the infarct-related coronary artery yields far better results in terms of limiting infarct size, maintenance of LV function, and reduction of both short- and long-term mortality rates. Additional methods of angiographic assessment of the efficacy of fibrinolysis include counting the number of frames on the cine film required for dye to flow from the origin

of the infarct-related artery to a landmark in the distal vascular bed (TIMI frame count) and determining the rate of entry and exit of contrast dye from the microvasculature in the myocardial infarct zone (TIMI myocardial perfusion grade). These methods have an even tighter correlation with outcomes after STEMI than the more commonly employed TIMI flow grade.

tPA and the other relatively fibrin-specific plasminogen activators, rPA and TNK, are more effective than streptokinase at restoring full perfusion—i.e., TIMI grade 3 coronary flow—and have a small edge in improving survival as well. The current recommended regimen of tPA consists of a 15-mg bolus followed by 50 mg intravenously over the first 30 min, followed by 35 mg over the next 60 min. Streptokinase is administered as 1.5 million units (MU) intravenously over 1 h. rPA is administered in a double-bolus regimen consisting of a 10-MU bolus given over 2–3 min, followed by a second 10-MU bolus 30 min later. TNK is given as a single weight-based intravenous bolus of 0.53 mg/kg over 10 s. In addition to the fibrinolytic agents discussed earlier, pharmacologic reperfusion typically involves adjunctive antiplatelet and antithrombotic drugs, as discussed subsequently.

Clear contraindications to the use of fibrinolytic agents include a history of cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (a reliably determined systolic arterial pressure >180 mmHg and/or a diastolic pressure >110 mmHg) at any time during the acute presentation, suspicion of aortic dissection, and active internal bleeding (excluding menses). While advanced age is associated with an increase in hemorrhagic complications, the benefit of fibrinolytic therapy in the elderly appears to justify its use if no other contraindications are present and the amount of myocardium in jeopardy appears to be substantial.

Relative contraindications to fibrinolytic therapy, which require assessment of the risk-to-benefit ratio, include current use of anti-coagulants (international normalized ratio ≥ 2), a recent (<2 weeks) invasive or surgical procedure or prolonged (>10 min) cardiopulmonary resuscitation, known bleeding diathesis, pregnancy, a hemorrhagic ophthalmic condition (e.g., hemorrhagic diabetic retinopathy), active peptic ulcer disease, and a history of severe hypertension that is currently adequately controlled. Because of the risk of an allergic reaction, patients should not receive streptokinase if that agent had been received within the preceding 5 days to 2 years.

Allergic reactions to streptokinase occur in $\approx 2\%$ of patients who receive it. While a minor degree of hypotension occurs in 4–10% of patients given this agent, marked hypotension occurs, although rarely, in association with severe allergic reactions.

Hemorrhage is the most frequent and potentially the most serious complication. Because bleeding episodes that require transfusion are more common when patients require invasive procedures, unnecessary venous or arterial interventions should be avoided in patients receiving fibrinolytic agents. Hemorrhagic stroke is the most serious complication and occurs in 0.5–0.9% of patients being treated with these agents. This rate increases with advancing age, with patients >70 years experiencing roughly twice the rate of intracranial hemorrhage as those <65 years. Large-scale trials have suggested that the rate of intracranial hemorrhage with tPA or rPA is slightly higher than with streptokinase.

INTEGRATED REPERFUSION STRATEGY

Evidence has emerged that suggests PCI plays an increasingly important role in the management of STEMI. Prior approaches that segregated the pharmacologic and catheter-based approaches to reperfusion have now been replaced with an integrated approach to triage and transfer of STEMI patients to receive PCI (Fig. 41-4). To achieve the degree of integration required to care for a patient with STEMI, all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of emergency medical services and hospital-based activities.

Cardiac catheterization and coronary angiography should be carried out after fibrinolytic therapy if there is evidence of either (1) failure of reperfusion (persistent chest pain and ST-segment elevation >90 min), in which case a rescue PCI should be considered; or (2) coronary artery reocclusion (re-elevation of ST segments and/or recurrent chest pain) or the development of recurrent ischemia (such as recurrent angina in the early hospital course or a positive exercise stress test before discharge), in which case an urgent PCI should be considered. Routine angiography and elective PCI even in asymptomatic patients following administration of fibrinolytic therapy are used with less frequency, given the numerous technologic advances that have occurred in the catheterization laboratory and the increasing number of skilled interventionalists. Coronary artery bypass surgery should be reserved for patients whose coronary anatomy is unsuited to PCI but in whom revascularization appears to be advisable because of extensive jeopardized myocardium or recurrent ischemia.

HOSPITAL PHASE MANAGEMENT

CORONARY CARE UNITS

These units are routinely equipped with a system that permits continuous monitoring of the cardiac rhythm

of each patient and hemodynamic monitoring in selected patients. Defibrillators, respirators, noninvasive transthoracic pacemakers, and facilities for introducing pacing catheters and flow-directed balloon-tipped catheters are also usually available. Equally important is the organization of a highly trained team of nurses who can recognize arrhythmias; adjust the dosage of antiarrhythmic, vasoactive, and anticoagulant drugs; and perform cardiac resuscitation, including electroshock, when necessary.

Patients should be admitted to a coronary care unit early in their illness when it is expected that they will derive benefit from the sophisticated and expensive care provided. The availability of electrocardiographic monitoring and trained personnel outside the coronary care unit has made it possible to admit lower-risk patients (e.g., those not hemodynamically compromised and without active arrhythmias) to “intermediate care units.”

The duration of stay in the coronary care unit is dictated by the ongoing need for intensive care. If symptoms are controlled with oral therapy, patients may be transferred out of the coronary care unit. Also, patients who have a confirmed STEMI but who are considered to be at low risk (no prior infarction and no persistent chest discomfort, CHF, hypotension, or cardiac arrhythmias) may be safely transferred out of the coronary care unit within 24 h.

Activity

Factors that increase the work of the heart during the initial hours of infarction may increase the size of the infarct. Therefore, patients with STEMI should be kept at bed rest for the first 6–12 h. However, in the absence of complications, patients should be encouraged, under supervision, to resume an upright posture by dangling their feet over the side of the bed and sitting in a chair within the first 24 h. This practice is psychologically beneficial and usually results in a reduction in the pulmonary capillary wedge pressure. In the absence of hypotension and other complications, by the second or third day, patients typically are ambulating in their room with increasing duration and frequency, and they may shower or stand at the sink to bathe. By day 3 after infarction, patients should be increasing their ambulation progressively to a goal of 185 m (600 ft) at least three times a day.

Diet

Because of the risk of emesis and aspiration soon after STEMI, patients should receive either nothing or only clear liquids by mouth for the first 4–12 h. The typical coronary care unit diet should provide ≤30% of total calories as fat and have a cholesterol content of ≤300 mg/d. Complex carbohydrates should make up 50–55% of total

calories. Portions should not be unusually large, and the menu should be enriched with foods that are high in potassium, magnesium, and fiber, but low in sodium. Diabetes mellitus and hypertriglyceridemia are managed by restriction of concentrated sweets in the diet.

Bowel management

Bed rest and the effect of the narcotics used for the relief of pain often lead to constipation. A bedside commode rather than a bedpan, a diet rich in bulk, and the routine use of a stool softener such as dioctyl sodium sulfosuccinate (200 mg/d) are recommended. If the patient remains constipated despite these measures, a laxative can be prescribed. Contrary to prior belief, it is safe to perform a gentle rectal examination on patients with STEMI.

Sedation

Many patients require sedation during hospitalization to withstand the period of enforced inactivity with tranquility. Diazepam (5 mg), oxazepam (15–30 mg), or lorazepam (0.5–2 mg), given three to four times daily, is usually effective. An additional dose of any of the above medications may be given at night to ensure adequate sleep. Attention to this problem is especially important during the first few days in the coronary care unit, where the atmosphere of 24-h vigilance may interfere with the patient's sleep. However, sedation is no substitute for reassuring, quiet surroundings. Many drugs used in the coronary care unit, such as atropine, H₂ blockers, and narcotics, can produce delirium, particularly in the elderly. This effect should not be confused with agitation, and it is wise to conduct a thorough review of the patient's medications before arbitrarily prescribing additional doses of anxiolytics.

PHARMACOTHERAPY

ANTITHROMBOTIC AGENTS

The use of antiplatelet and anticoagulant therapy during the initial phase of STEMI is based on extensive laboratory and clinical evidence that thrombosis plays an important role in the pathogenesis of this condition. The primary goal of treatment with antiplatelet and anticoagulant agents is to maintain patency of the infarct-related artery, in conjunction with reperfusion strategies. A secondary goal is to reduce the patient's tendency to thrombosis and, thus, the likelihood of mural thrombus formation or deep venous thrombosis, either of which could result in pulmonary embolization. The degree to which antiplatelet and anticoagulant therapy achieves these goals partly

determines how effectively it reduces the risk of mortality from STEMI.

As noted previously (see "Management in the Emergency Department" earlier), aspirin is the standard antiplatelet agent for patients with STEMI. The most compelling evidence for the benefits of antiplatelet therapy (mainly with aspirin) in STEMI is found in the comprehensive overview by the Antiplatelet Trialists' Collaboration. Data from nearly 20,000 patients with MI enrolled in 15 randomized trials were pooled and revealed a relative reduction of 27% in the mortality rate, from 14.2% in control patients to 10.4% in patients receiving antiplatelet agents.

Inhibitors of the P2Y₁₂ ADP receptor prevent activation and aggregation of platelets. The addition of the P2Y₁₂ inhibitor clopidogrel to background treatment with aspirin to STEMI patients reduces the risk of clinical events (death, reinfarction, stroke) and, in patients receiving fibrinolytic therapy, has been shown to prevent reocclusion of a successfully reperfused infarct artery. New P2Y₁₂ ADP receptor antagonists, such as prasugrel and ticagrelor, are more effective than clopidogrel in preventing ischemic complications in STEMI patients undergoing PCI, but are associated with an increased risk of bleeding. Glycoprotein IIb/IIIa receptor inhibitors appear useful for preventing thrombotic complications in patients with STEMI undergoing PCI.

The standard anticoagulant agent used in clinical practice is unfractionated heparin (UFH). The available data suggest that when UFH is added to a regimen of aspirin and a non-fibrin-specific thrombolytic agent such as streptokinase, additional mortality benefit occurs (about 5 lives saved per 1000 patients treated). It appears that the immediate administration of intravenous UFH, in addition to a regimen of aspirin and relatively fibrin-specific fibrinolytic agents (tPA, rPA, or TNK), helps to maintain patency of the infarct-related artery. This effect is achieved at the cost of a small increased risk of bleeding. The recommended dose of UFH is an initial bolus of 60 U/kg (maximum 4000 U) followed by an initial infusion of 12 U/kg per hour (maximum 1000 U/h). The activated partial thromboplastin time during maintenance therapy should be 1.5–2 times the control value.

Alternatives to UFH for anticoagulation of patients with STEMI are the low-molecular-weight heparin (LMWH) preparations, a synthetic version of the critical pentasaccharide sequence (fondaparinux), and the direct antithrombin bivalirudin. Advantages of LMWHs include high bioavailability permitting administration subcutaneously, reliable anticoagulation without monitoring, and greater antiXa:IIa activity. Enoxaparin has been shown to reduce significantly the composite endpoints of death/nonfatal reinfarction and death/nonfatal reinfarction/urgent

revascularization compared with UFH in STEMI patients who receive fibrinolysis. Treatment with enoxaparin is associated with higher rates of serious bleeding, but net clinical benefit—a composite endpoint that combines efficacy and safety—still favors enoxaparin over UFH. Interpretation of the data on fondaparinux is difficult because of the complex nature of the pivotal clinical trial evaluating it in STEMI (OASIS-6). Fondaparinux appears superior to placebo in STEMI patients not receiving reperfusion therapy, but its relative efficacy and safety compared with UFH is less certain. Due to the risk of catheter thrombosis, fondaparinux should not be used alone at the time of coronary angiography and PCI but should be combined with another anticoagulant with antithrombin activity such as UFH or bivalirudin. Contemporary trials of bivalirudin used an open-label design to evaluate its efficacy and safety compared with UFH plus a glycoprotein IIb/IIIa inhibitor. Bivalirudin was associated with a lower rate of bleeding, largely driven by reductions in vascular access site hematomas ≥ 5 cm or the administration of blood transfusions.

Patients with an anterior location of the infarction, severe LV dysfunction, heart failure, a history of embolism, two-dimensional echocardiographic evidence of mural thrombus, or atrial fibrillation are at increased risk of systemic or pulmonary thromboembolism. Such individuals should receive full therapeutic levels of anticoagulant therapy (LMWH or UFH) while hospitalized, followed by at least 3 months of warfarin therapy.

BETA-ADRENOCEPTOR BLOCKERS

The benefits of beta blockers in patients with STEMI can be divided into those that occur immediately when the drug is given acutely and those that accrue over the long term when the drug is given for secondary prevention after an infarction. Acute intravenous beta blockade improves the myocardial O_2 supply-demand relationship, decreases pain, reduces infarct size, and decreases the incidence of serious ventricular arrhythmias. In patients who undergo fibrinolysis soon after the onset of chest pain, no incremental reduction in mortality rate is seen with beta blockers, but recurrent ischemia and reinfarction are reduced.

Thus, beta-blocker therapy after STEMI is useful for most patients (including those treated with an angiotensin-converting enzyme [ACE] inhibitor) except those in whom it is specifically contraindicated (patients with heart failure or severely compromised LV function, heart block, orthostatic hypotension, or a history of asthma) and perhaps those whose excellent long-term prognosis (defined as an expected mortality rate of $<1\%$ per year, patients <55 years, no previous MI, with normal ventricular function, no complex

ventricular ectopy, and no angina) markedly diminishes any potential benefit.

INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

ACE inhibitors reduce the mortality rate after STEMI, and the mortality benefits are additive to those achieved with aspirin and beta blockers. The maximum benefit is seen in high-risk patients (those who are elderly or who have an anterior infarction, a prior infarction, and/or globally depressed LV function), but evidence suggests that a short-term benefit occurs when ACE inhibitors are prescribed unselectively to all hemodynamically stable patients with STEMI (i.e., those with a systolic pressure >100 mmHg). The mechanism involves a reduction in ventricular remodeling after infarction (see “Ventricular Dysfunction” later) with a subsequent reduction in the risk of CHF. The rate of recurrent infarction may also be lower in patients treated chronically with ACE inhibitors after infarction.

Before hospital discharge, LV function should be assessed with an imaging study. ACE inhibitors should be continued indefinitely in patients who have clinically evident CHF, in patients in whom an imaging study shows a reduction in global LV function or a large regional wall motion abnormality, or in those who are hypertensive.

Angiotensin receptor blockers (ARBs) should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiologic signs of heart failure. Long-term aldosterone blockade should be prescribed for STEMI patients without significant renal dysfunction (creatinine ≥ 2.5 mg/dL in men and ≥ 2.0 mg/dL in women) or hyperkalemia (potassium ≥ 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LV ejection fraction $\leq 40\%$, and have either symptomatic heart failure or diabetes mellitus. A multidrug regimen for inhibiting the renin-angiotensin-aldosterone system has been shown to reduce both heart failure-related and sudden cardiac death-related cardiovascular mortality after STEMI, but has not been as thoroughly explored as ACE inhibitors in STEMI patients.

OTHER AGENTS

Favorable effects on the ischemic process and ventricular remodeling (see below) previously led many physicians to routinely use intravenous nitroglycerin (5–10 $\mu\text{g}/\text{min}$ initial dose and up to 200 $\mu\text{g}/\text{min}$ as long as hemodynamic stability is maintained) for the first 24–48 h after the onset of infarction. However, the benefits of routine use of intravenous nitroglycerin are less in the contemporary era where beta-adrenoceptor

blockers and ACE inhibitors are routinely prescribed for patients with STEMI.

Results of multiple trials of different calcium antagonists have failed to establish a role for these agents in the treatment of most patients with STEMI. Therefore, the routine use of calcium antagonists cannot be recommended. Strict control of blood glucose in diabetic patients with STEMI has been shown to reduce the mortality rate. Serum magnesium should be measured in all patients on admission, and any demonstrated deficits should be corrected to minimize the risk of arrhythmias.

COMPLICATIONS AND THEIR MANAGEMENT

VENTRICULAR DYSFUNCTION

After STEMI, the left ventricle undergoes a series of changes in shape, size, and thickness in both the infarcted and noninfarcted segments. This process is referred to as ventricular remodeling and generally precedes the development of clinically evident CHF in the months to years after infarction. Soon after STEMI, the left ventricle begins to dilate. Acutely, this results from expansion of the infarct, i.e., slippage of muscle bundles, disruption of normal myocardial cells, and tissue loss within the necrotic zone, resulting in disproportionate thinning and elongation of the infarct zone. Later, lengthening of the noninfarcted segments occurs as well. The overall chamber enlargement that occurs is related to the size and location of the infarct, with greater dilation following infarction of the anterior wall and apex of the left ventricle and causing more marked hemodynamic impairment, more frequent heart failure, and a poorer prognosis. Progressive dilation and its clinical consequences may be ameliorated by therapy with ACE inhibitors and other vasodilators (e.g., nitrates). In patients with an ejection fraction $<40\%$, regardless of whether or not heart failure is present, ACE inhibitors or ARBs should be prescribed (see “Inhibition of the Renin-Angiotensin-Aldosterone System” earlier).

HEMODYNAMIC ASSESSMENT

Pump failure is now the primary cause of in-hospital death from STEMI. The extent of infarction correlates well with the degree of pump failure and with mortality, both early (within 10 days of infarction) and later. The most common clinical signs are pulmonary rales and S_3 and S_4 gallop sounds. Pulmonary congestion is also frequently seen on the chest roentgenogram. Elevated

LV filling pressure and elevated pulmonary artery pressure are the characteristic hemodynamic findings, but these findings may result from a reduction of ventricular compliance (diastolic failure) and/or a reduction of stroke volume with secondary cardiac dilation (systolic failure) (**Chap. 19**).

A classification originally proposed by Killip divides patients into four groups: class I, no signs of pulmonary or venous congestion; class II, moderate heart failure as evidenced by rales at the lung bases, S_3 gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion; class III, severe heart failure, pulmonary edema; and class IV, shock with systolic pressure <90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion, and oliguria. When this classification was established in 1967, the expected hospital mortality rate of patients in these classes was as follows: class I, 0–5%; class II, 10–20%; class III, 35–45%; and class IV, 85–95%. With advances in management, the mortality rate in each class has fallen, perhaps by as much as one-third to one-half.

Hemodynamic evidence of abnormal global LV function appears when contraction is seriously impaired in 20–25% of the left ventricle. Infarction of $\geq 40\%$ of the left ventricle usually results in cardiogenic shock (**Chap. 34**). Positioning of a balloon flotation (Swan-Ganz) catheter in the pulmonary artery permits monitoring of LV filling pressure; this technique is useful in patients who exhibit hypotension and/or clinical evidence of CHF. Cardiac output can also be determined with a pulmonary artery catheter. With the addition of intra-arterial pressure monitoring, systemic vascular resistance can be calculated as a guide to adjusting vasopressor and vasodilator therapy. Some patients with STEMI have markedly elevated LV filling pressures (>22 mmHg) and normal cardiac indices ($2.6\text{--}3.6$ L/[min/m²]), while others have relatively low LV filling pressures (<15 mmHg) and reduced cardiac indices. The former patients usually benefit from diuresis, while the latter may respond to volume expansion.

HYPOVOLEMIA

This is an easily corrected condition that may contribute to the hypotension and vascular collapse associated with STEMI in some patients. It may be secondary to previous diuretic use, to reduced fluid intake during the early stages of the illness, and/or to vomiting associated with pain or medications. Consequently, hypovolemia should be identified and corrected in patients with STEMI and hypotension before more vigorous forms of therapy are begun. Central venous pressure reflects RV rather than LV filling pressure and is an inadequate guide for adjustment of blood volume, because LV

function is almost always affected much more adversely than RV function in patients with STEMI. The optimal LV filling or pulmonary artery wedge pressure may vary considerably among patients. Each patient's ideal level (generally ≤ 20 mmHg) is reached by cautious fluid administration during careful monitoring of oxygenation and cardiac output. Eventually, the cardiac output level plateaus, and further increases in LV filling pressure only increase congestive symptoms and decrease systemic oxygenation without raising arterial pressure.

TREATMENT Congestive Heart Failure

The management of CHF in association with STEMI is similar to that of acute heart failure secondary to other forms of heart disease (avoidance of hypoxemia, diuresis, afterload reduction, inotropic support) (**Chap. 19**), except that the benefits of digitalis administration to patients with STEMI are unimpressive. By contrast, diuretic agents are extremely effective, as they diminish pulmonary congestion in the presence of systolic and/or diastolic heart failure. LV filling pressure falls and orthopnea and dyspnea improve after the intravenous administration of furosemide or other loop diuretics. These drugs should be used with caution, however, as they can result in a massive diuresis with associated decreases in plasma volume, cardiac output, systemic blood pressure, and, hence, coronary perfusion. Nitrates in various forms may be used to decrease preload and congestive symptoms. Oral isosorbide dinitrate, topical nitroglycerin ointment, and intravenous nitroglycerin all have the advantage over a diuretic of lowering preload through venodilation without decreasing the total plasma volume. In addition, nitrates may improve ventricular compliance if ischemia is present, as ischemia causes an elevation of LV filling pressure. Vasodilators must be used with caution to prevent serious hypotension. As noted earlier, ACE inhibitors are an ideal class of drugs for management of ventricular dysfunction after STEMI, especially for the long term. (See "Inhibition of the Renin-Angiotensin-Aldosterone System" earlier.)

CARDIOGENIC SHOCK

Prompt reperfusion, efforts to reduce infarct size and treatment of ongoing ischemia and other complications of MI appear to have reduced the incidence of cardiogenic shock from 20% to about 7%. Only 10% of patients with this condition present with it on admission, while 90% develop it during hospitalization. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease with evidence of "piecemeal" necrosis extending outward from the original infarct zone. **The evaluation and management of cardiogenic shock and severe power failure after STEMI are discussed in detail in Chap. 34.**

RIGHT VENTRICULAR INFARCTION

Approximately one-third of patients with inferior infarction demonstrate at least a minor degree of RV necrosis. An occasional patient with inferoposterior LV infarction also has extensive RV infarction, and rare patients present with infarction limited primarily to the RV. Clinically significant RV infarction causes signs of severe RV failure (jugular venous distention, Kussmaul's sign, hepatomegaly [**Chap. 9**]) with or without hypotension. ST-segment elevations of right-sided precordial ECG leads, particularly lead V_4R , are frequently present in the first 24 h in patients with RV infarction. Two-dimensional echocardiography is helpful in determining the degree of RV dysfunction. Catheterization of the right side of the heart often reveals a distinctive hemodynamic pattern resembling constrictive pericarditis (steep right atrial "y" descent and an early diastolic dip and plateau in RV waveforms) (**Chap. 28**). Therapy consists of volume expansion to maintain adequate RV preload and efforts to improve LV performance with attendant reduction in pulmonary capillary wedge and pulmonary arterial pressures.

ARRHYTHMIAS

(See also **Chaps. 15 and 17**) The incidence of arrhythmias after STEMI is higher in patients seen early after the onset of symptoms. The mechanisms responsible for infarction-related arrhythmias include autonomic nervous system imbalance, electrolyte disturbances, ischemia, and slowed conduction in zones of ischemic myocardium. An arrhythmia can usually be managed successfully if trained personnel and appropriate equipment are available when it develops. Since most deaths from arrhythmia occur during the first few hours after infarction, the effectiveness of treatment relates directly to the speed with which patients come under medical observation. The prompt management of arrhythmias constitutes a significant advance in the treatment of STEMI.

Ventricular premature beats

Infrequent, sporadic ventricular premature depolarizations occur in almost all patients with STEMI and do not require therapy. Whereas in the past, frequent, multifocal, or early diastolic ventricular extrasystoles (so-called warning arrhythmias) were routinely treated with antiarrhythmic drugs to reduce the risk of development of ventricular tachycardia and ventricular fibrillation, pharmacologic therapy is now reserved for patients with sustained ventricular arrhythmias. Prophylactic antiarrhythmic therapy (either intravenous lidocaine early or oral agents later) is contraindicated for ventricular premature beats in the absence of clinically important ventricular tachyarrhythmias, because such therapy

may actually increase the mortality rate. Beta-adrenoceptor blocking agents are effective in abolishing ventricular ectopic activity in patients with STEMI and in the prevention of ventricular fibrillation. As described earlier (see “Beta-Adrenoceptor Blockers”), they should be used routinely in patients without contraindications. In addition, hypokalemia and hypomagnesemia are risk factors for ventricular fibrillation in patients with STEMI; to reduce the risk, the serum potassium concentration should be adjusted to approximately 4.5 mmol/L and magnesium to about 2.0 mmol/L.

Ventricular tachycardia and fibrillation

Within the first 24 h of STEMI, ventricular tachycardia and fibrillation can occur without prior warning arrhythmias. The occurrence of ventricular fibrillation can be reduced by prophylactic administration of intravenous lidocaine. However, prophylactic use of lidocaine has not been shown to reduce overall mortality from STEMI. In fact, in addition to causing possible noncardiac complications, lidocaine may predispose to an excess risk of bradycardia and asystole. For these reasons, and with earlier treatment of active ischemia, more frequent use of beta-blocking agents, and the nearly universal success of electrical cardioversion or defibrillation, routine prophylactic antiarrhythmic drug therapy is no longer recommended.

Sustained ventricular tachycardia that is well tolerated hemodynamically should be treated with an intravenous regimen of amiodarone (bolus of 150 mg over 10 min, followed by infusion of 1.0 mg/min for 6 h and then 0.5 mg/min) or procainamide (bolus of 15 mg/kg over 20–30 min; infusion of 1–4 mg/min); if it does not stop promptly, electroversion should be used (**Chap. 17**). An unsynchronized discharge of 200–300 J (monophasic waveform; approximately 50% of these energies with biphasic waveforms) is used immediately in patients with ventricular fibrillation or when ventricular tachycardia causes hemodynamic deterioration. Ventricular tachycardia or fibrillation that is refractory to electroshock may be more responsive after the patient is treated with epinephrine (1 mg intravenously or 10 mL of a 1:10,000 solution via the intracardiac route) or amiodarone (a 75–150-mg bolus).

Ventricular arrhythmias, including the unusual form of ventricular tachycardia known as torsades des pointes (**Chaps. 17 and 18**), may occur in patients with STEMI as a consequence of other concurrent problems (such as hypoxia, hypokalemia, or other electrolyte disturbances) or of the toxic effects of an agent being administered to the patient (such as digoxin or quinidine). A search for such secondary causes should always be undertaken.

Although the in-hospital mortality rate is increased, the long-term survival is excellent in patients who survive to hospital discharge after primary ventricular

fibrillation; i.e., ventricular fibrillation that is a primary response to acute ischemia that occurs during the first 48 h and is not associated with predisposing factors such as CHF, shock, bundle branch block, or ventricular aneurysm. This result is in sharp contrast to the poor prognosis for patients who develop ventricular fibrillation secondary to severe pump failure. For patients who develop ventricular tachycardia or ventricular fibrillation late in their hospital course (i.e., after the first 48 h), the mortality rate is increased both in-hospital and during long-term follow-up. Such patients should be considered for electrophysiologic study and implantation of a cardioverter-defibrillator (ICD) (**Chap. 17**). A more challenging issue is the prevention of sudden cardiac death from ventricular fibrillation late after STEMI in patients who have not exhibited sustained ventricular tachyarrhythmias during their index hospitalization. An algorithm for selection of patients who warrant prophylactic implantation of an ICD is shown in **Fig. 41-5**.

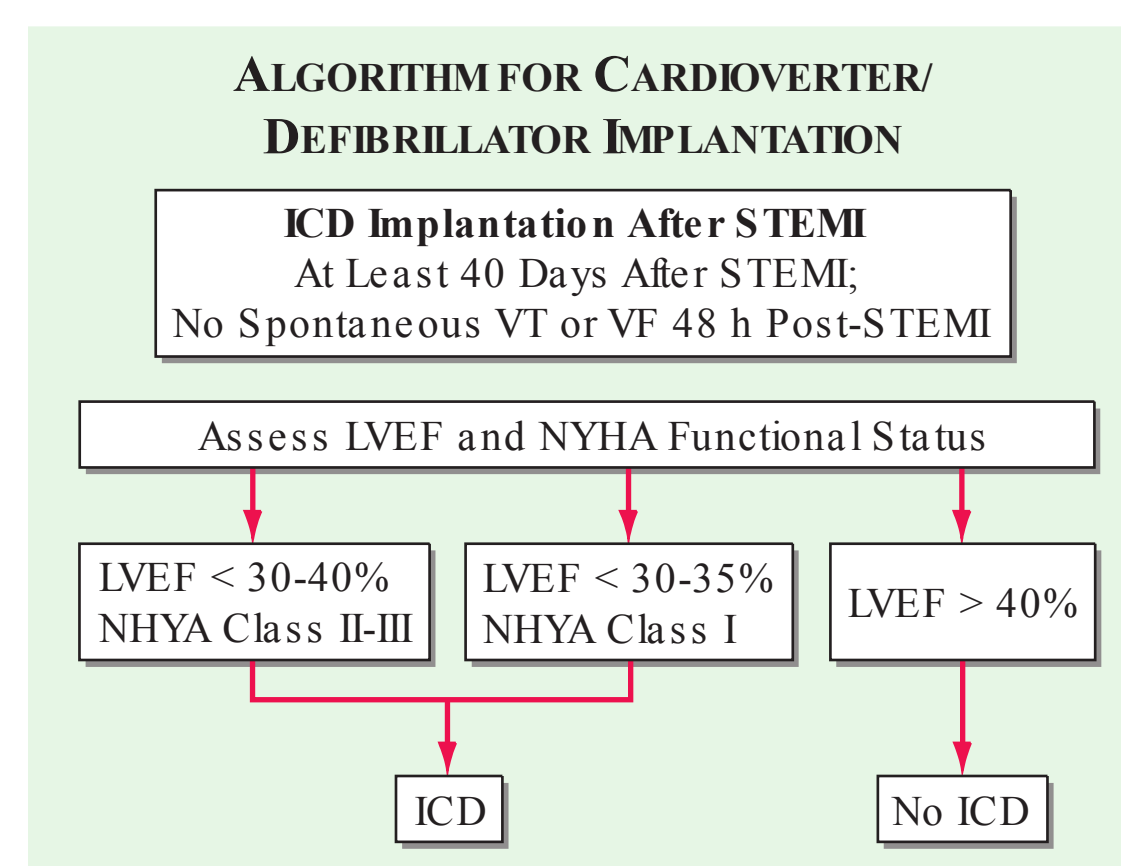


FIGURE 41-5

Algorithm for assessment of need for implantation of a cardioverter-defibrillator. The appropriate management is selected based on measurement of left ventricular ejection fraction and assessment of the New York Heart Association (NYHA) functional class. Patients with depressed left ventricular function at least 40 days after ST-segment elevation myocardial infarction (STEMI) are referred for insertion of an implantable cardioverter-defibrillator (ICD) if the left ventricular ejection fraction (LVEF) is <30–40% and they are in NYHA class II–III or if the LVEF is <30–35% and they are in NYHA class I functional status. Patients with preserved left ventricular function (LVEF >40%) do not receive an ICD regardless of NYHA functional class. All patients are treated with medical therapy after STEMI. VF, ventricular fibrillation; VT, ventricular tachycardia. (Adapted from data contained in DP Zipes et al: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death; a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines [Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death]. J Am Coll Cardiol 48:1064, 2006.)

Accelerated idioventricular rhythm

Accelerated idioventricular rhythm (AIVR, “slow ventricular tachycardia”), a ventricular rhythm with a rate of 60–100 beats/min, often occurs transiently during fibrinolytic therapy at the time of reperfusion. For the most part, AIVR, whether it occurs in association with fibrinolytic therapy or spontaneously, is benign and does not presage the development of classic ventricular tachycardia. Most episodes of AIVR do not require treatment if the patient is monitored carefully, as degeneration into a more serious arrhythmia is rare.

Supraventricular arrhythmias

Sinus tachycardia is the most common supraventricular arrhythmia. If it occurs secondary to another cause (such as anemia, fever, heart failure, or a metabolic derangement), the primary problem should be treated first. However, if it appears to be due to sympathetic overstimulation (e.g., as part of a hyperdynamic state), then treatment with a beta blocker is indicated. Other common arrhythmias in this group are atrial flutter and atrial fibrillation, which are often secondary to LV failure. Digoxin is usually the treatment of choice for supraventricular arrhythmias if heart failure is present. If heart failure is absent, beta blockers, verapamil, or diltiazem are suitable alternatives for controlling the ventricular rate, as they may also help to control ischemia. If the abnormal rhythm persists for >2 h with a ventricular rate >120 beats/min, or if tachycardia induces heart failure, shock, or ischemia (as manifested by recurrent pain or ECG changes), a synchronized electroshock (100–200 J monophasic waveform) should be used.

Accelerated junctional rhythms have diverse causes but may occur in patients with inferoposterior infarction. Digitalis excess must be ruled out. In some patients with severely compromised LV function, the loss of appropriately timed atrial systole results in a marked reduction of cardiac output. Right atrial or coronary sinus pacing is indicated in such instances.

Sinus Bradycardia

Treatment of sinus bradycardia is indicated if hemodynamic compromise results from the slow heart rate. Atropine is the most useful drug for increasing heart rate and should be given intravenously in doses of 0.5 mg initially. If the rate remains <50–60 beats/min, additional doses of 0.2 mg, up to a total of 2.0 mg, may be given. Persistent bradycardia (<40 beats/min) despite atropine may be treated with electrical pacing. Isoproterenol should be avoided.

Atrioventricular and intraventricular conduction disturbances

(See also Chap. 15) Both the in-hospital mortality rate and the postdischarge mortality rate of patients who

have complete atrioventricular (AV) block in association with anterior infarction are markedly higher than those of patients who develop AV block with inferior infarction. This difference is related to the fact that heart block in inferior infarction is commonly a result of increased vagal tone and/or the release of adenosine and therefore is transient. In anterior wall infarction, however, heart block is usually related to ischemic malfunction of the conduction system, which is commonly associated with extensive myocardial necrosis.

Temporary electrical pacing provides an effective means of increasing the heart rate of patients with bradycardia due to AV block. However, acceleration of the heart rate may have only a limited impact on prognosis in patients with anterior wall infarction and complete heart block in whom the large size of the infarct is the major factor determining outcome. It should be carried out if it improves hemodynamics. Pacing does appear to be beneficial in patients with inferoposterior infarction who have complete heart block associated with heart failure, hypotension, marked bradycardia, or significant ventricular ectopic activity. A subgroup of these patients, those with RV infarction, often respond poorly to ventricular pacing because of the loss of the atrial contribution to ventricular filling. In such patients, dual-chamber AV sequential pacing may be required.

External noninvasive pacing electrodes should be positioned in a “demand” mode for patients with sinus bradycardia (rate <50 beats/min) that is unresponsive to drug therapy, Mobitz II second-degree AV block, third-degree heart block, or bilateral bundle branch block (e.g., right bundle branch block plus left anterior fascicular block). Retrospective studies suggest that permanent pacing may reduce the long-term risk of sudden death due to bradyarrhythmias in the rare patient who develops combined persistent bifascicular and transient third-degree heart block during the acute phase of MI.

OTHER COMPLICATIONS

Recurrent chest discomfort

Because recurrent or persistent ischemia often heralds extension of the original infarct or reinfarction in a new myocardial zone and is associated with a near tripling of mortality after STEMI, patients with these symptoms should be referred for prompt coronary arteriography and mechanical revascularization. Administration of a fibrinolytic agent is an alternative to early mechanical revascularization.

Pericarditis

(See also Chap. 28) Pericardial friction rubs and/or pericardial pain are frequently encountered in patients with STEMI involving the epicardium. This complication can usually be managed with aspirin (650 mg four

times daily). It is important to diagnose the chest pain of pericarditis accurately, because failure to recognize it may lead to the erroneous diagnosis of recurrent ischemic pain and/or infarct extension, with resulting inappropriate use of anticoagulants, nitrates, beta blockers, or coronary arteriography. When it occurs, complaints of pain radiating to either trapezius muscle is helpful, because such a pattern of discomfort is typical of pericarditis but rarely occurs with ischemic discomfort. Anticoagulants potentially could cause tamponade in the presence of acute pericarditis (as manifested by either pain or persistent rub) and therefore should not be used unless there is a compelling indication.

Thromboembolism

Clinically apparent thromboembolism complicates STEMI in $\approx 10\%$ of cases, but embolic lesions are found in 20% of patients in necropsy series, suggesting that thromboembolism is often clinically silent. Thromboembolism is considered to be an important contributing cause of death in 25% of patients with STEMI who die after admission to the hospital. Arterial emboli originate from LV mural thrombi, while most pulmonary emboli arise in the leg veins.

Thromboembolism typically occurs in association with large infarcts (especially anterior), CHF, and an LV thrombus detected by echocardiography. The incidence of arterial embolism from a clot originating in the ventricle at the site of an infarction is small but real. Two-dimensional echocardiography reveals LV thrombi in about one-third of patients with anterior wall infarction but in few patients with inferior or posterior infarction. Arterial embolism often presents as a major complication, such as hemiparesis when the cerebral circulation is involved or hypertension if the renal circulation is compromised. When a thrombus has been clearly demonstrated by echocardiographic or other techniques or when a large area of regional wall motion abnormality is seen even in the absence of a detectable mural thrombus, systemic anticoagulation should be undertaken (in the absence of contraindications), as the incidence of embolic complications appears to be markedly lowered by such therapy. The appropriate duration of therapy is unknown, but 3–6 months is probably prudent.

Left ventricular aneurysm

The term ventricular aneurysm is usually used to describe dyskinesis or local expansile paradoxical wall motion. Normally functioning myocardial fibers must shorten more if stroke volume and cardiac output are to be maintained in patients with ventricular aneurysm; if they cannot, overall ventricular function is impaired. True aneurysms are composed of scar tissue and neither predispose to nor are associated with cardiac rupture.

The complications of LV aneurysm do not usually occur for weeks to months after STEMI; they include CHF, arterial embolism, and ventricular arrhythmias. Apical aneurysms are the most common and the most easily detected by clinical examination. The physical finding of greatest value is a double, diffuse, or displaced apical impulse. Ventricular aneurysms are readily detected by two-dimensional echocardiography, which may also reveal a mural thrombus in an aneurysm.

Rarely, myocardial rupture may be contained by a local area of pericardium, along with organizing thrombus and hematoma. Over time, this pseudoaneurysm enlarges, maintaining communication with the LV cavity through a narrow neck. Because a pseudoaneurysm often ruptures spontaneously, it should be surgically repaired if recognized.

POSTINFARCTION RISK STRATIFICATION AND MANAGEMENT

Many clinical and laboratory factors have been identified that are associated with an increase in cardiovascular risk after initial recovery from STEMI. Some of the most important factors include persistent ischemia (spontaneous or provoked), depressed LV ejection fraction ($<40\%$), rales above the lung bases on physical examination or congestion on chest radiograph, and symptomatic ventricular arrhythmias. Other features associated with increased risk include a history of previous MI, age >75 , diabetes mellitus, prolonged sinus tachycardia, hypotension, ST-segment changes at rest without angina (“silent ischemia”), an abnormal signal-averaged ECG, nonpatency of the infarct-related coronary artery (if angiography is undertaken), and persistent advanced heart block or a new intraventricular conduction abnormality on the ECG. Therapy must be individualized on the basis of the relative importance of the risk(s) present.

The goal of preventing reinfarction and death after recovery from STEMI has led to strategies to evaluate risk after infarction. In stable patients, submaximal exercise stress testing may be carried out before hospital discharge to detect residual ischemia and ventricular ectopy and to provide the patient with a guideline for exercise in the early recovery period. Alternatively, or in addition, a maximal (symptom-limited) exercise stress test may be carried out 4–6 weeks after infarction. Evaluation of LV function is usually warranted as well. Recognition of a depressed LV ejection fraction by echocardiography or radionuclide ventriculography identifies patients who should receive medications to inhibit the renin-angiotensin-aldosterone system. Patients in whom angina is induced at relatively low

workloads, those who have a large reversible defect on perfusion imaging or a depressed ejection fraction, those with demonstrable ischemia, and those in whom exercise provokes symptomatic ventricular arrhythmias should be considered at high risk for recurrent MI or death from arrhythmia (Fig. 41-5). Cardiac catheterization with coronary angiography and/or invasive electrophysiologic evaluation is advised.

Exercise tests also aid in formulating an individualized exercise prescription, which can be much more vigorous in patients who tolerate exercise without any of the previously mentioned adverse signs. In addition, predischARGE stress testing may provide an important psychological benefit, building the patient's confidence by demonstrating a reasonable exercise tolerance.

In many hospitals, a cardiac rehabilitation program with progressive exercise is initiated in the hospital and continued after discharge. Ideally, such programs should include an educational component that informs patients about their disease and its risk factors.

The usual duration of hospitalization for an uncomplicated STEMI is about 5 days. The remainder of the convalescent phase may be accomplished at home. During the first 1–2 weeks, the patient should be encouraged to increase activity by walking about the house and outdoors in good weather. Normal sexual activity may be resumed during this period. After 2 weeks, the physician must regulate the patient's activity on the basis of exercise tolerance. Most patients will be able to return to work within 2–4 weeks.

SECONDARY PREVENTION

Various secondary preventive measures are at least partly responsible for the improvement in the long-term mortality and morbidity rates after STEMI. Long-term treatment with an antiplatelet agent (usually aspirin) after STEMI is associated with a 25% reduction in the risk of recurrent infarction, stroke,

or cardiovascular mortality (36 fewer events for every 1000 patients treated). An alternative antiplatelet agent that may be used for secondary prevention in patients intolerant of aspirin is clopidogrel (75 mg orally daily). ACE inhibitors or ARBs and, in appropriate patients, aldosterone antagonists should be used indefinitely by patients with clinically evident heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality to prevent late ventricular remodeling and recurrent ischemic events.

The chronic routine use of oral beta-adrenoceptor blockers for at least 2 years after STEMI is supported by well-conducted, placebo-controlled trials.

Evidence suggests that warfarin lowers the risk of late mortality and the incidence of reinfarction after STEMI. Most physicians prescribe aspirin routinely for all patients without contraindications and add warfarin for patients at increased risk of embolism (see “Thromboembolism” earlier). Several studies suggest that in patients <75 years old a low dose of aspirin (75–81 mg/d) in combination with warfarin administered to achieve an international normalized ratio >2.0 is more effective than aspirin alone for preventing recurrent MI and embolic cerebrovascular accident. However, there is an increased risk of bleeding and a high rate of discontinuation of warfarin that has limited clinical acceptance of combination antithrombotic therapy. There is increased risk of bleeding when warfarin is added to dual antiplatelet therapy (aspirin and clopidogrel). However, patients who have had a stent implanted and have an indication for anticoagulation should receive dual antiplatelet therapies in combination with warfarin. Such patients should also receive a proton pump inhibitor to minimize the risk of gastrointestinal bleeding and should have regular monitoring of their hemoglobin levels and stool hematest while on combination antithrombotic therapy.

Finally, risk factors for atherosclerosis (**Chap. 1**) should be discussed with the patient and, when possible, favorably modified.

CHAPTER 42

PERCUTANEOUS CORONARY INTERVENTIONS AND OTHER INTERVENTIONAL PROCEDURES

David P. Faxon ■ Deepak L. Bhatt

Percutaneous transluminal coronary angioplasty (PTCA) was first introduced by Andreas Gruentzig in 1977 as an alternative to coronary bypass surgery. The concept was initially demonstrated by Charles Dotter in 1964 in peripheral vessels. The development of a small inelastic balloon catheter by Gruentzig allowed expansion of the technique into smaller peripheral and coronary vessels. Initial coronary experience was limited to single-vessel coronary disease and discrete proximal lesions due to the technical limitations of the equipment. Advances in technology and greater operator experience allowed the procedure to grow rapidly with expanded use in patients with more complex lesions and multivessel disease. The introduction of coronary stents in 1994 was one of the major advances in the field. These devices reduced acute complications and reduced by half the significant problem of restenosis (or recurrence of the stenosis). Further reductions in restenosis were achieved by the introduction of drug-eluting stents in 2003. These stents slowly release antiproliferative drugs directly into the plaque over a few months. Percutaneous coronary intervention (PCI) is the most common revascularization procedure in the United States and is performed more than twice as often as coronary artery bypass surgery: nearly 600,000 patients a year.

Interventional cardiology is a separate discipline in cardiology that requires a dedicated 1-year interventional cardiology fellowship following a 3-year general cardiology fellowship in order to obtain a separate board certification. The discipline has also expanded to include interventions for structural heart disease including treatment of congenital heart disease and valvular heart disease; it also includes interventions to treat peripheral vascular disease, including atherosclerotic and nonatherosclerotic lesions in the carotid, renal, aortic, and peripheral circulations.

TECHNIQUE

The initial procedure is performed in a similar manner as a diagnostic cardiac catheterization (**Chap. 13**). Arterial access is obtained via the femoral or radial artery. To prevent thrombotic complications during the procedure, patients who are anticipated to need an angioplasty are given aspirin (325 mg) and may be given clopidogrel (loading dose of 300–600 mg), prasugrel (loading dose of 60 mg), or ticagrelor (loading dose of 180 mg) before the procedure. During the procedure, anticoagulation is achieved by administration of unfractionated heparin, enoxaparin (a low-molecular-weight heparin), or bivalirudin (a direct thrombin inhibitor). The latter has gained popularity due to the significant reduction in bleeding complications. In patients with ST-elevation myocardial infarction, high-risk acute coronary syndrome, or a large thrombus in the coronary artery, an intravenous glycoprotein IIb/IIIa inhibitor (abciximab, tirofiban, or eptifibatide) may also be given.

Following placement of an introducing sheath, preformed guiding catheters are used to cannulate selectively the origins of the coronary arteries. Through the guiding catheter, a flexible, steerable guidewire is negotiated down the coronary artery lumen using fluoroscopic guidance; it is then advanced through the stenosis and into the vessel beyond. This guidewire then serves as a “rail” over which angioplasty balloons, stents, or other therapeutic devices can be advanced to enlarge the narrowed segment of coronary artery. The artery is usually dilated with a balloon catheter followed by placement of a stent. The catheters and introducing sheath are removed and the artery manually held or closed using one of several femoral arterial closure devices to achieve hemostasis. Because PCI is performed under local anesthesia and mild sedation, it requires only a short (1-day) hospitalization or less.

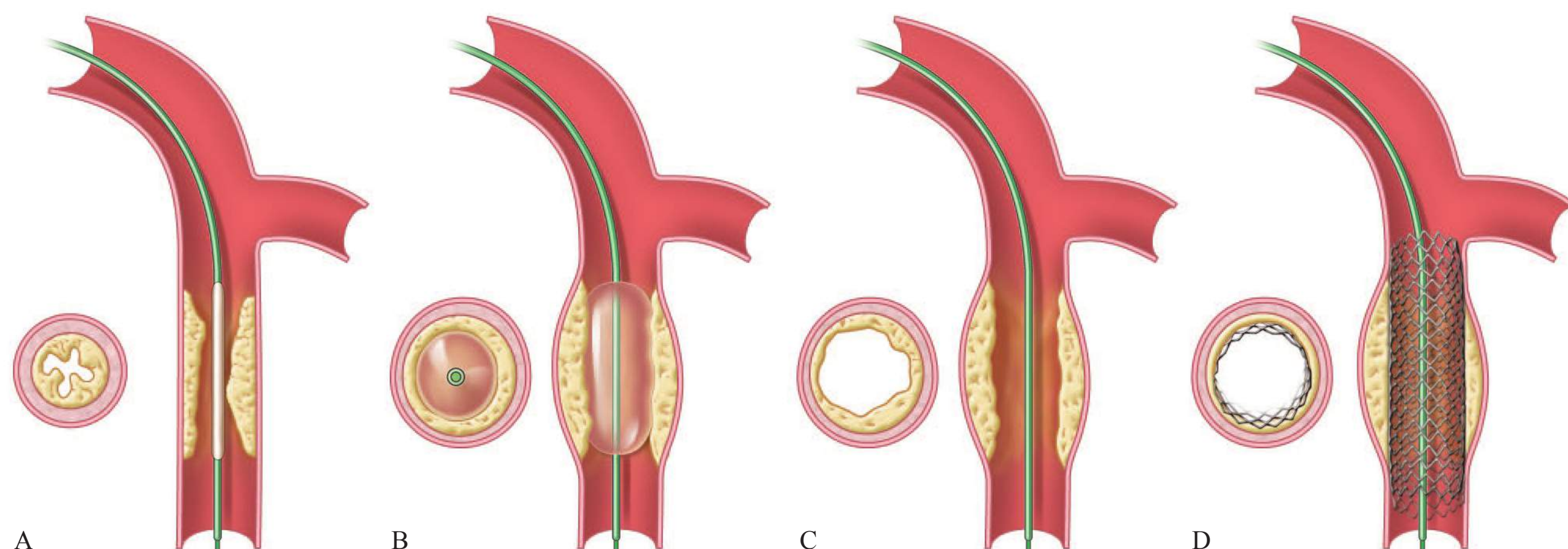


FIGURE 42-1

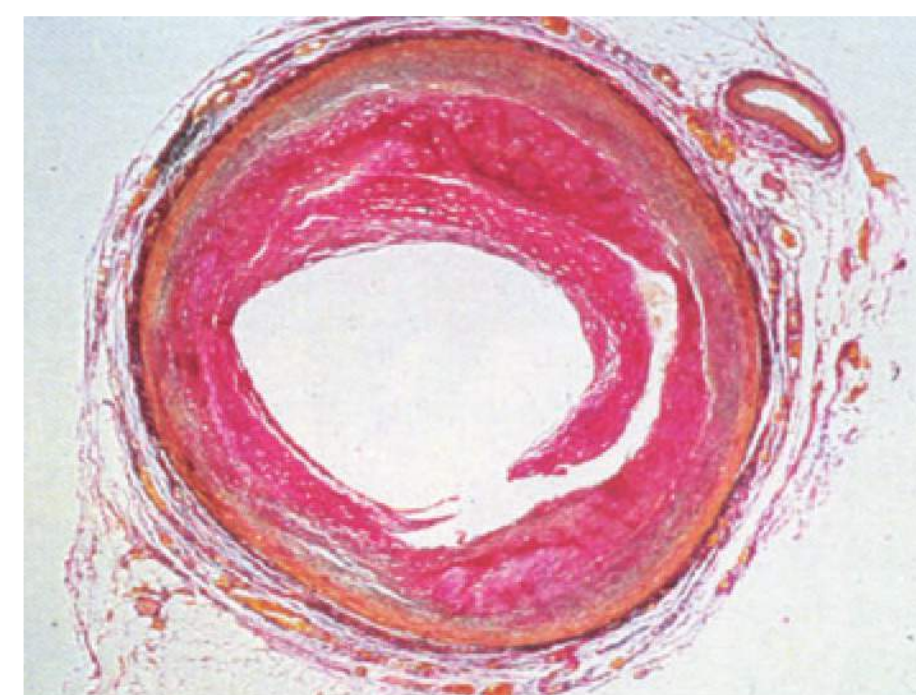
Schematic diagram of the primary mechanisms of balloon angioplasty and stenting. A. A balloon angioplasty catheter is positioned into the stenosis over a guidewire under fluoroscopic guidance. B. The balloon is inflated temporarily occluding the vessel. C. The lumen is enlarged primarily by stretching the vessel, often resulting in small dissections in the neointima. D. A stent mounted on a deflated balloon is placed into the lesion

and pressed against the vessel wall with balloon inflation (not shown). The balloon is deflated and removed, leaving the stent permanently against the wall acting as a scaffold to hold the dissections against the wall and prevent vessel recoil. (Adapted from EJ Topol: Textbook of Cardiovascular Medicine, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2002.)

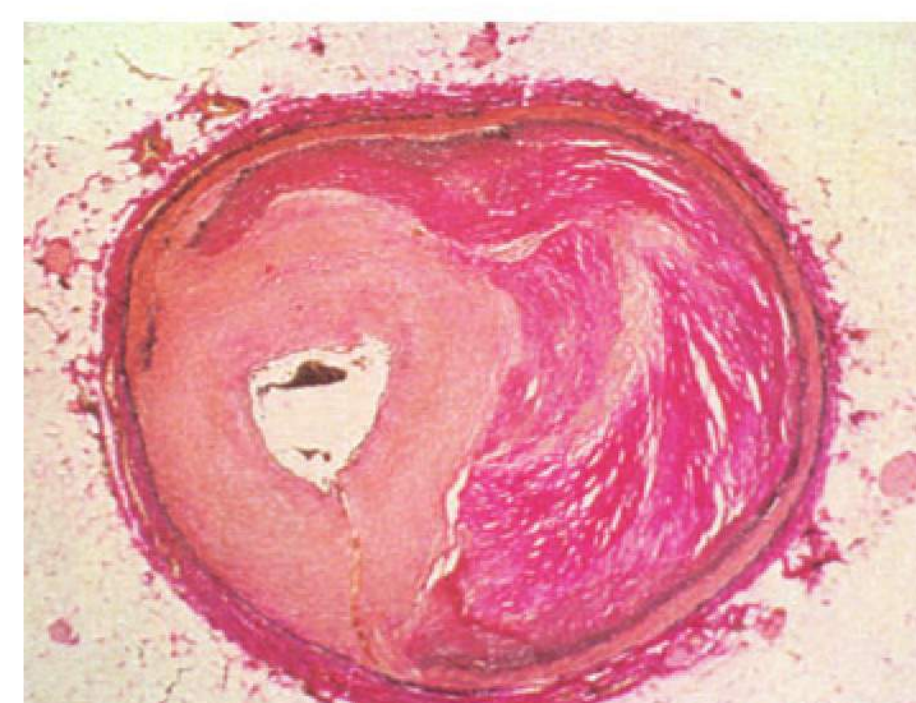
Angioplasty works by stretching the artery and displacing the plaque away from the lumen, enlarging the entire vessel (Figs. 42-1 and 42-2). The procedure rarely results in embolization of atherosclerotic material. Owing to inelastic elements in the plaque, the stretching of the vessel by the balloon results in small localized dissections that can protrude into the lumen and be a nidus for acute thrombus formation. If the dissections are severe, then they can obstruct the lumen or induce a thrombotic occlusion of the artery (acute closure). Stents have largely prevented this complication by holding the dissection flaps up against the vessel wall (Fig. 42-1).

Stents are currently used in more than 90% of coronary angioplasty procedures. Stents are wire meshes (usually made of stainless steel) that are compressed over a deflated angioplasty balloon. When the balloon is inflated, the stent is enlarged to approximate the “normal” vessel lumen. The balloon is then deflated and removed, leaving the stent behind to provide a permanent scaffold in the artery. Owing to the design of the struts, these devices are flexible, allowing their passage through diseased and tortuous coronary vessels. Stents are rigid enough to prevent elastic recoil of the vessel and have dramatically improved the success and safety of the procedure as a result.

Drug-eluting stents further enhanced the efficacy of PCI. An antiproliferative agent is attached to the metal stent by use of a thin polymer coating. The antiproliferative drug elutes from the stent over a 1- to 3-month



A



B

FIGURE 42-2

Pathology of acute effects of balloon angioplasty with intimal dissection and vessel stretching (A) and an example of neointimal hyperplasia and restenosis showing renarrowing of the vessel (B). (Panel A from M Ueda et al: Eur Heart J 12:937, 1991; with permission. Panel B from CE Essed et al: Br Heart J 49:393, 1983; with permission.)

period after implantation. Drug-eluting stents have been shown to reduce clinical restenosis by 50%, so that in uncomplicated lesions symptomatic restenosis occurs in 5–10% of patients. Not surprisingly, this led to the rapid acceptance of these devices; currently 80–90% of all stents implanted are drug-eluting. The first-generation devices were coated with either sirolimus or paclitaxel. Second-generation drug-eluting stents use newer agents such as everolimus, biolimus, and zotarolimus. These second-generation drug-eluting stents appear to be more effective with fewer complications, such as early or late stent thrombosis, than the first-generation devices and, therefore, have replaced the first-generation stents. Biodegradable polymers that are used to attach the drugs to the stents may be superior to permanent polymers in preventing late stent thrombosis and are under investigation. In addition, the everolimus-eluting biodegradable vascular scaffold (BVS) stent has been shown to be safe and effective with gradual degradation over several years with return of normal vessel function. It is currently approved in Europe. Additional stents are under investigation. Other interventional devices include atherectomy devices and thrombectomy catheters. These devices are designed to remove atherosclerotic plaque or thrombus and are used in conjunction with balloon dilatation and stent placement. Rotational atherectomy is the most commonly used adjunctive device and is modeled after a dentist's drill, with small round burrs of 1.25–2.5 mm at the tip of a flexible wire shaft. They are passed over the guidewire up to the stenosis and drill away atherosclerotic material. Because the atherosclerotic particles are ≤ 25 μm , they pass through the coronary microcirculation and rarely cause problems. The device is particularly useful in heavily calcified plaques that are resistant to balloon dilatation. Given the current advances in stents, rotational atherectomy is infrequently used. Directional atherectomy catheters are not used in the coronaries any longer but are used in peripheral arterial disease. In acute ST-elevation myocardial infarction, specialized catheters without a balloon are used to aspirate thrombus in order to prevent embolization down the coronary vessel and to improve blood flow before angioplasty and stent placement. Some data suggest that manual catheter thrombus aspiration may reduce mortality in addition to improving blood flow in primary PCI.

PCI of degenerated saphenous vein graft lesions has been associated with a significant incidence of distal embolization of atherosclerotic material, unlike PCI of native vessel disease. A number of distal protection devices have been shown to significantly reduce embolization and myocardial infarction in this setting. Most devices work by using a collapsible wire filter at the end of a guidewire that is expanded in the distal vessel before PCI. If atherosclerotic debris is dislodged,

the basket captures the material, and at the end of the PCI, the basket is pulled into a delivery catheter and the debris safely removed from the patient.

SUCCESS AND COMPLICATIONS

A successful procedure (angiographic success), defined as a reduction of the stenosis to less than a 20% diameter narrowing, occurs in 95–99% of patients. Lower success rates are seen in patients with tortuous, small, or calcified vessels or chronic total occlusions. Chronic total occlusions have the lowest success rates (60–70%), and their recanalization is usually not attempted unless the occlusion is recent (within 3 months) or there are favorable anatomic features. Improvements in equipment and technique have increased the success rates of recanalization of chronic total occlusions.

Serious complications are rare but include a mortality rate of 0.1–0.3% for elective cases, a large myocardial infarction in less than 3%, and stroke in less than 0.1%. Patients who are elderly (>65 years), undergoing an emergent or urgent procedure, have chronic kidney disease, present with an ST-segment elevation myocardial infarction (STEMI), or are in shock have significantly higher risk. Scoring systems can help to estimate the risk of the procedure. Myocardial infarction during PCI can occur for multiple reasons including an acute occluding thrombus, severe coronary dissection, embolization of thrombus or atherosclerotic material, or closure of a side branch vessel at the site of angioplasty. Most myocardial infarctions are small and only detected by a rise in the creatine phosphokinase (CPK) or troponin level after the procedure. Only those with significant enzyme elevations (more than three to five times the upper limit of normal) are associated with a less favorable long-term outcome. Coronary stents have largely prevented coronary dissections due to the scaffolding effect of the stent.

Metallic stents are also prone to stent thrombosis (1–3%), either acute (<24 h) or subacute (1–30 days), which can be ameliorated by greater attention to full initial stent deployment and the use of dual antiplatelet therapy (DAPT) (aspirin, plus a platelet P2Y₁₂ receptor blocker [clopidogrel, prasugrel, or ticagrelor]). Late (30 days–1 year) and very late stent thromboses (>1 year) occur very infrequently with stents but are slightly more common with first-generation drug-eluting stents, necessitating DAPT for up to 1 year or longer. Use of the second-generation stents is associated with lower rates of late and very late stent thromboses, and shorter durations of DAPT may be possible. Premature discontinuation of DAPT, particularly in the first month after implantation, is associated with a significantly increased risk for stent thrombosis (three- to ninefold

greater). Stent thrombosis results in death in 10–20% and myocardial infarction in 30–70% of patients. Elective surgery that requires discontinuation of antiplatelet therapy after drug-eluting stent implantation should be postponed until after 6 months and preferably after 1 year, if at all possible.

Restenosis, or renarrowing of the dilated coronary stenosis, is the most common complication of angioplasty and occurs in 20–50% of patients with balloon angioplasty alone, 10–30% of patients with bare metal stents, and 5–15% of patients with drug-eluting stents within the first year. The fact that stent placement provides a larger acute luminal area than balloon angioplasty alone reduces the incidence of subsequent restenosis. Drug-eluting stents further reduce restenosis through a reduction in excessive neointimal growth over the stent. If restenosis does not occur, the long-term outcome is excellent (**Fig. 42-3**). Clinical restenosis is recognized by recurrence of angina or symptoms within 9 months of the procedure. Less frequently, patients with restenosis can present with non-ST-segment elevation myocardial infarction (NSTEMI) (10%) or STEMI (2%) as well. Clinical restenosis requires confirmation of a significant stenosis at the site of the prior PCI. Target lesion revascularization (TLR) or target vessel revascularization (TVR) is defined as angiographic restenosis with repeat PCI or coronary artery bypass grafting (CABG). By angiography, the incidence of restenosis is significantly higher than clinical restenosis (TLR or TVR) because many patients have mild

restenosis that does not result in a recurrence of symptoms. The management of clinical restenosis is usually to repeat the PCI with balloon dilatation and placement of a drug-eluting stent. Once a patient has had restenosis, the risk of a second restenosis is further increased. The risk factors for restenosis are diabetes, myocardial infarction, long lesions, small-diameter vessels, and suboptimal initial PCI result.

INDICATIONS

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines extensively review the indications for PCI in patients with stable angina, unstable angina, NSTEMI, and STEMI and should be referred to for a comprehensive discussion of the indications. Briefly, the two principal indications for coronary revascularization in patients with chronic stable angina (**Chap. 39**) are (1) to improve anginal symptoms in patients who remain symptomatic despite adequate medical therapy and (2) to reduce mortality rates in patients with severe coronary disease. In patients with stable angina who are well controlled on medical therapy, studies such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trials have shown that initial revascularization does not lead to better outcomes and can be safely delayed until symptoms worsen or evidence of severe ischemia

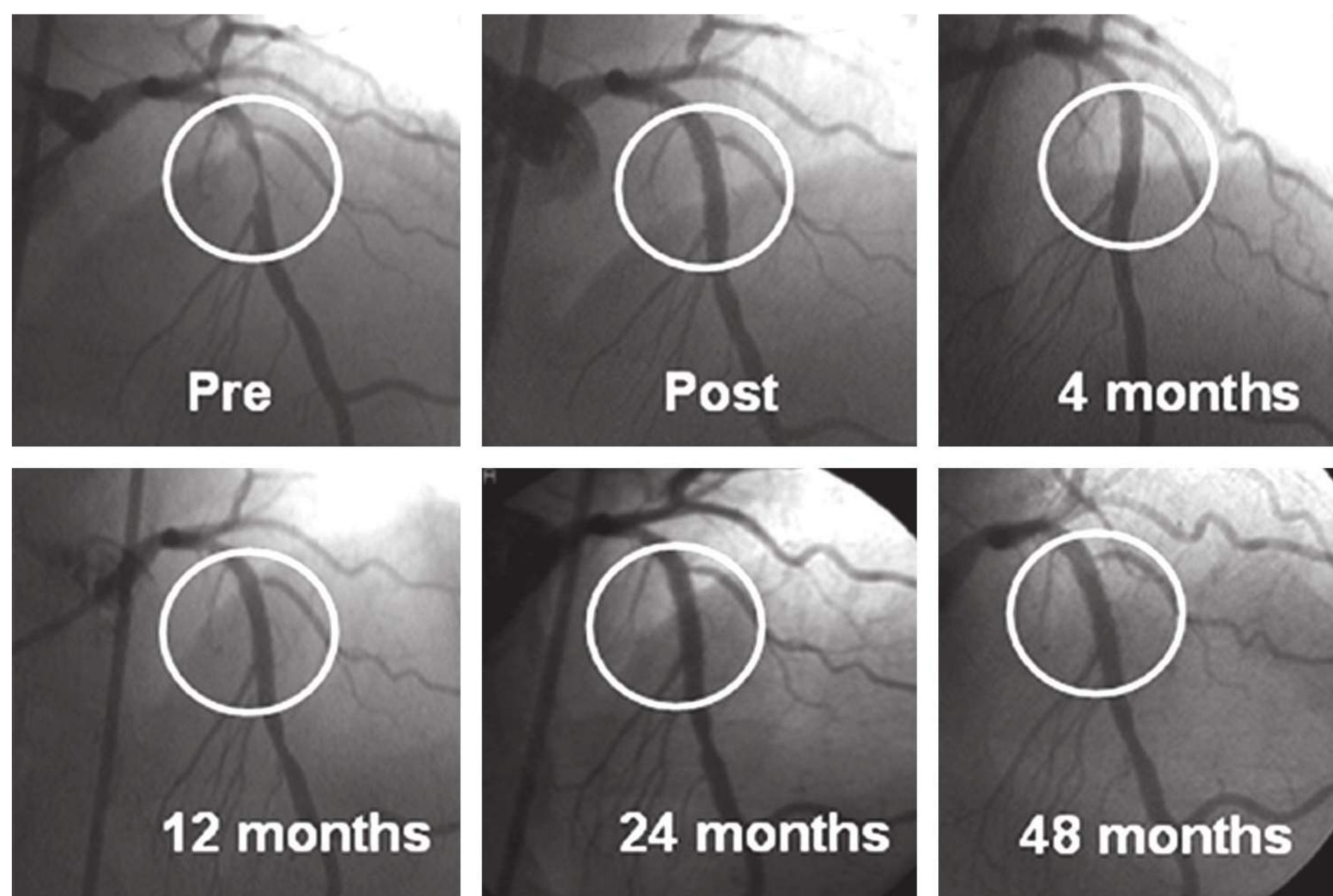


FIGURE 42-3

Long-term results from one of the first patients to receive a sirolimus-eluting stent from early Sao Paulo experience. (From: GW Stone, in D Baim [ed]: Cardiac Catheterization, Angiography

and Intervention, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2006; with permission.)

on noninvasive testing occurs. When revascularization is indicated, the choice of PCI or CABG depends on a number of clinical and anatomic factors (**Fig. 42-4**). The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial compared PCI with the paclitaxel drug-eluting stent to CABG in 1800 patients with three-vessel coronary disease or left main disease. The study found no difference in death or myocardial infarction at 1 year, but repeat revascularization was significantly higher in the stent-treated group (13.5 vs. 5.9%), while stroke was significantly higher in the surgical group (2.2 vs. 0.6%). The primary endpoint of death, myocardial infarction, stroke, or revascularization was significantly better with CABG, particularly in those with the most extensive coronary artery disease. The 3-year results confirm these findings. The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 patients with diabetes and multivessel disease and showed a significantly lower primary endpoint of death, myocardial infarction, or stroke with CABG than

PCI. These studies support CABG for those with the most severe left main and three-vessel disease or those with diabetes. Lesser degrees of multivessel disease in patients with or without diabetes have an equal outcome with PCI.

The choice of PCI versus CABG is also related to the anticipated procedural success and complications of PCI and the risks of CABG. For PCI, the characteristics of the coronary anatomy are critically important. The location of the lesion in the vessel (proximal or distal), the degree of tortuosity, and the size of the vessel are considered. In addition, the lesion characteristics, including the degree of the stenosis, the presence of calcium, lesion length, and presence of thrombus, are assessed. The most common reason to decide not to do PCI is that the lesion felt to be responsible for the patient's symptoms is not treatable. This is most commonly due to the presence of a chronic total occlusion (>3 months in duration). In this setting, the historical success rate has been low (30–70%) and complications are more common. A lesion classification to characterize the likelihood of success or failure of PCI has been developed by the ACC/AHA. Lesions with the highest success are called type A lesions (such as proximal noncalcified subtotal lesions), and those with the lowest success or highest complication rate are type C lesions (such as chronic total occlusions). Intermediate lesions are classified as type B1 or B2 depending on the number of unfavorable characteristics. Approximately 25–30% of patients will not be candidates for PCI due to unfavorable anatomy, whereas only 5% of CABG patients will not be candidates for surgery due to coronary anatomy. The primary reason for being considered inoperable with CABG is the presence of severe comorbidities such as advanced age, frailty, severe chronic obstructive pulmonary disease (COPD), or poor left ventricular function.

Another consideration in choosing a revascularization strategy is the degree of revascularization. In patients with multivessel disease, bypass grafts can usually be placed to all vessels with significant stenosis, whereas PCI may be able to treat only some of the lesions due to the presence of unfavorable anatomy. Assessment of the significance of intermediate lesions using fractional flow reserve (FFR) (**Chap. 13**) can assist in determining which lesions should be revascularized. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial showed a 30% reduction in adverse events when revascularization by PCI was restricted to those lesions that were hemodynamically significant ($\text{FFR} \leq 0.80$) rather than when guided by angiography alone. Thus, complete revascularization of all functionally significant lesions should be favored and considered when choosing the optimal revascularization strategy. Given the multiple factors

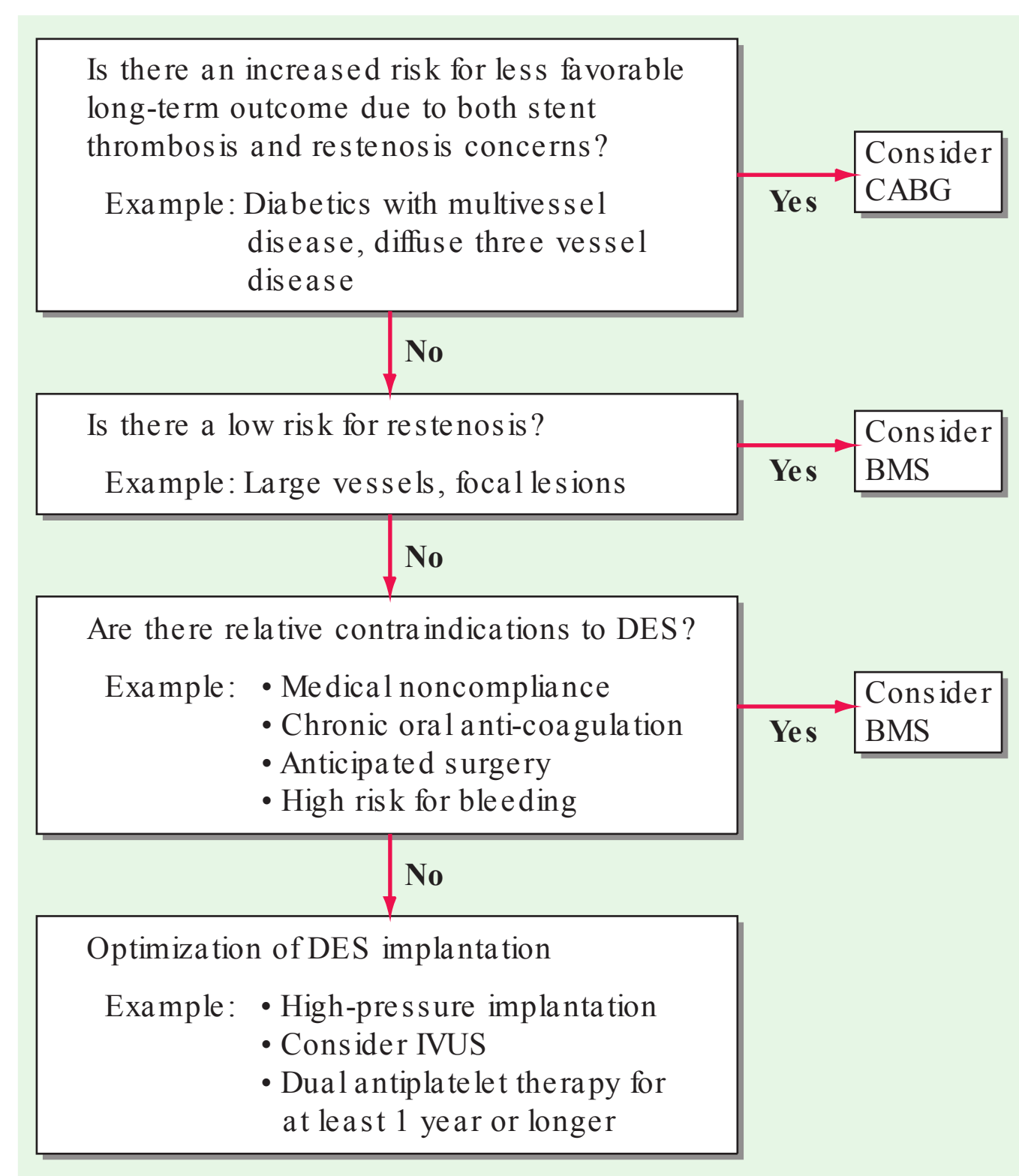


FIGURE 42-4

In patients requiring revascularization, several factors need to be considered in choosing between bare metal stents, drug-eluting stents, or coronary artery bypass surgery. ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; IVUS, intravascular ultrasound; STEMI, ST-segment elevation myocardial infarction. (From AA Bavry, DL Bhatt: *Circulation* 116:696, 2007; with permission.)

that need to be considered in choosing the best revascularization for an individual patient with multivessel disease, it is optimal to have a discussion among the cardiac surgeon, interventional cardiologist, and the physicians caring for the patient (so-called Heart Team) to properly weigh the choices.

Patients with acute coronary syndrome are at excess risk of short- and long-term mortality. Randomized clinical trials have shown that PCI is superior to intensive medical therapy in reducing mortality and myocardial infarction, with the benefit largely confined to those patients who are high risk. High-risk patients are defined as those with any one of the following: refractory ischemia, recurrent angina, positive cardiac-specific enzymes, new ST-segment depression, low ejection fraction, severe arrhythmias, or a recent PCI or CABG. PCI is preferred over surgical therapy in most high-risk patients with acute coronary syndromes unless they have severe multivessel disease or the culprit lesion responsible for the unstable presentation cannot be adequately treated. In STEMI, thrombolysis or PCI (primary PCI) are effective methods to restore coronary blood flow and salvage myocardium within the first 12 h after onset of chest pain. Because PCI is more effective in restoring flow than thrombolysis, it is preferred if readily available. PCI is also performed following thrombolysis to facilitate adequate reperfusion or as a rescue procedure in those who do not achieve reperfusion from thrombolysis or in those who develop cardiogenic shock.

OTHER INTERVENTIONAL TECHNIQUES

Structural heart disease

Interventional treatment for structural heart disease (adult congenital heart disease and valvular heart disease) is a significant and growing component of the field of interventional cardiology.

The most common adult congenital lesion to be treated with percutaneous techniques is closure of atrial septal defects (**Chap. 22**). The procedure is done as in a diagnostic right heart catheterization with the passage of a catheter up the femoral vein into the right atrium. With echo and fluoroscopic guidance, the size and location of the defect can be accurately defined, and closure is accomplished using one of several approved devices. All devices use a left atrial and right atrial wire mesh or covered disk that are pulled together to capture the atrial septum around the defect and seal it off. The Amplatzer Septal Occluder device (AGA Medical, Minneapolis, Minnesota) is the most commonly used in the United States. The success rate in selected patients is 85–95%, and the device complications are rare and include device embolization, infection, or erosion. Closure of patent foramen ovale (PFO) is done in a similar way. PFO

closure may be considered in patients who have had recurrent paradoxical stroke or transient ischemic attack (TIA) despite adequate medical therapy including anticoagulation or antiplatelet therapy. The benefit, however, has not been proven. The CLOSURE I trial randomized 909 patients with cryptogenic stroke or TIA who had a PFO. Closure did not reduce the primary endpoint of death within 30 days or death following a neurologic cause during 2 years of follow-up or stroke/TIA within 2 years. Other trials have confirmed these findings. The use in the treatment of migraine is under clinical investigation and is not an approved indication.

Similar devices can also be used to close patent ductus arteriosus and ventricular septal defects. Other congenital diseases that can be treated percutaneously include coarctation of the aorta, pulmonic stenosis, peripheral pulmonary stenosis, and other abnormal communications between the cardiac chambers or vessels.

The treatment of valvular heart disease is the most rapidly growing area in interventional cardiology. Until recently, the only available techniques were balloon valvuloplasty for the treatment of aortic, mitral, or pulmonic stenosis (**Chap. 23**). Mitral valvuloplasty is the preferred treatment for symptomatic patients with rheumatic mitral stenosis who have favorable anatomy. The outcome in these patients is equal to that of surgical commissurotomy. The success is highly related to the echocardiographic appearance of the valve. The most favorable setting is commissural fusion without calcification or subchordal fusion and the absence of significant mitral regurgitation. Access is obtained from the femoral vein using a transseptal technique in which a long metal catheter with a needle tip is advanced from the femoral vein through the right atrium and atrial septum at the level of the foramen ovale into the left atrium. A guidewire is advanced into the left ventricle, and a balloon-dilatation catheter is negotiated across the mitral valve and inflated to a predetermined size to enlarge the valve. The most commonly used dilatation catheter is the Inoue balloon. The technique splits the commissural fusion and commonly results in a doubling of the mitral valve area. The success of the procedure in favorable anatomy is 95% and severe complications are rare (1–2%). The most common complications are tamponade due to puncture into the pericardium or the creation of severe mitral regurgitation.

For regurgitant valvular lesions, only severe mitral regurgitation can be effectively treated percutaneously using the MitraClip (Abbott, Abbott Park, Ill) device. The procedure involves the passage of a catheter into the left atrium using the transseptal technique. A special catheter with a metallic clip on the end is passed through the mitral valve and retracted to catch and clip

together the mid portion of the anterior and posterior mitral valve leaflet. The clip creates a double opening in the mitral valve and thereby reduces mitral regurgitation similar to the surgical Alfieri repair. In the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) trial, the device was less effective than surgical repair or replacement but was shown to be safe. It is currently used for patients who are not good candidates for surgical repair, particularly when the regurgitation is due to functional causes.

Severe aortic stenosis can be treated with balloon valvuloplasty as well. In this setting, the valvuloplasty balloon catheter is placed retrograde across the aortic valve from the femoral artery and briefly inflated to stretch open the valve. The success is much less favorable, with only 50% achieving an aortic valve area of $>1 \text{ cm}^2$ and a restenosis rate of 25–50% after 6–12 months. This poor success rate has limited its use to patients who are not surgical candidates or as a bridge to surgery or transcatheter aortic valve replacement (TAVR). In this setting, the intermediate-term mortality rate of the procedure is high (10%). Repeat aortic valvuloplasty as a treatment for aortic valve restenosis has been reported.

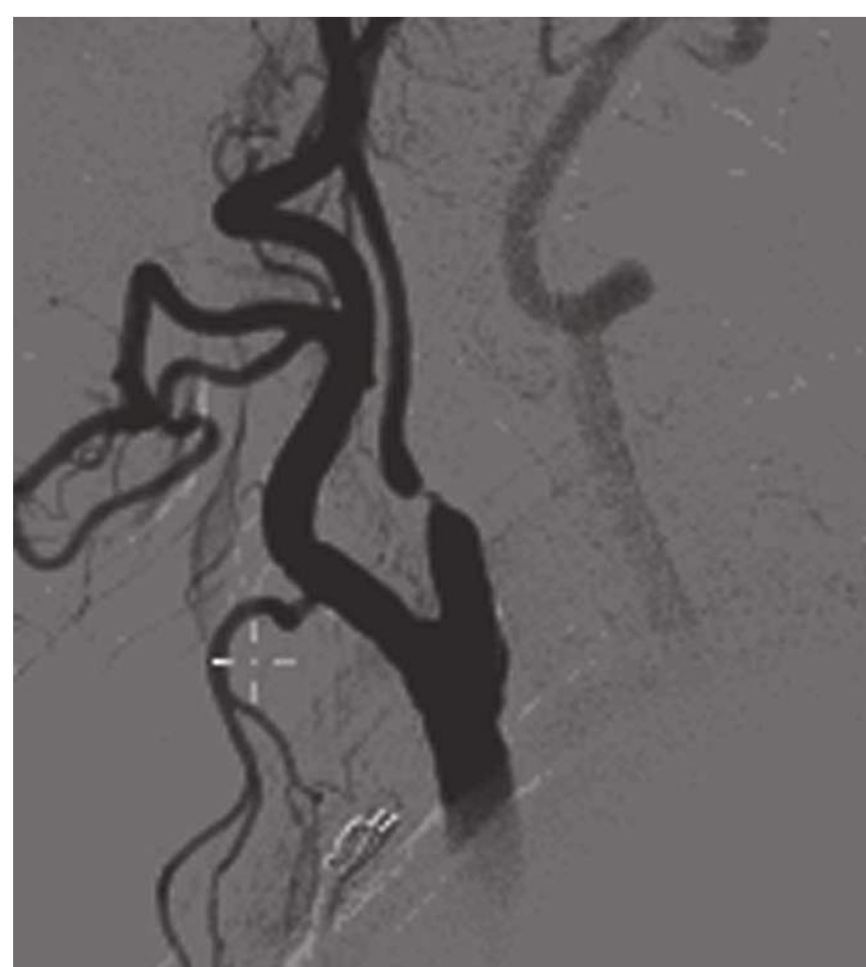
Percutaneous aortic valve replacement (TAVR) has been shown to be an effective treatment for high-risk and inoperable patients with aortic stenosis. Currently, two valve models, the Edwards SAPIEN valve (Edwards Lifescience, Irvine, California) and the CoreValve ReValving system (Medtronic, Minneapolis, Minnesota) are available. In more than 10,000 cases worldwide, follow-up shows no evidence of restenosis or severe prosthetic valve dysfunction in the midterm. The CoreValve is self-expanding, while the Edwards valve is balloon

expanded. The cannulas are large (14–22 French), and retrograde access via the femoral artery is most commonly chosen, if possible. In patients with peripheral artery disease, access via the subclavian artery or transapically through a surgical incision can be used. Following balloon valvuloplasty, the valve is positioned across the valve and deployed with postdeployment balloon inflation to ensure full contact with the aortic annulus. The success rate is 80–90%, and the 30-day mortality rate is 10–15%, not unexpectedly as only high-risk patients are undergoing the procedure currently. The Placement of Aortic Transcatheter Valve (PARTNER) randomized trial of the Edwards valve showed a 55% reduction in 1-year mortality and major adverse events in the extreme-risk group randomized to TAVR compared to medical therapy. In a separate randomized trial, high-risk patients had a similar outcome to surgical valve replacement at 1 year. As a result, this valve is approved for both high-risk and extreme-risk patients with severe aortic stenosis.

Pulmonic stenosis can also be effectively treated with balloon valvuloplasty and percutaneously replaced with the Melody stent (Medtronic). Tricuspid valve interventions remain experimental.

PERIPHERAL ARTERY INTERVENTIONS

The use of percutaneous interventions to treat symptomatic patients with arterial obstruction in the carotid, renal, aortic, and peripheral vessels is also part of the field of interventional cardiology. Randomized clinical trial data already support the use of carotid stenting in patients at high risk of complications from carotid endarterectomy (**Fig. 42-5**). Recent trials suggest similar



A



B

FIGURE 42-5

An example of a high-risk patient who requires carotid revascularization, but who is not a candidate for carotid endarterectomy. Carotid artery stenting resulted in an excellent

angiographic result. (From M Belkin, DL Bhatt: *Circulation* 119:2302, 2009; with permission.)

outcomes with carotid stenting and carotid endarterectomy in patients at average risk, although depending on the patient's risk for periprocedural stroke or myocardial infarction, one procedure may be preferred over the other. The success rate of peripheral artery interventional procedures has been improving, including for long segments of occlusive disease historically treated by peripheral bypass surgery (**Fig. 42-6**). Peripheral intervention is increasingly part of the training of an interventional cardiologist, and most programs now require an additional year of training after the interventional cardiology training year. The techniques and outcomes are described in detail in the chapter on peripheral vascular disease (**Chap. 47**).

Circulatory support techniques

The use of circulatory support techniques is occasionally needed in order to safely perform PCI on hemodynamically unstable patients. It also can be useful in helping to stabilize patients before surgical interventions. The most commonly used device is the percutaneous intraaortic balloon pump developed in the early 1960s. A 7- to 10-French, 25- to 50-mL balloon catheter is placed retrograde from the femoral artery into the descending aorta between the aortic arch and the abdominal aortic bifurcation. It is connected to a helium gas inflation system that synchronizes the

inflation to coincide with early diastole with deflation by mid-diastole. As a result, it increases early diastolic pressure, lowers systolic pressure, and lowers late diastolic pressure through displacement of blood from the descending aorta (counterpulsation). This results in an increase in coronary blood flow and a decrease in afterload. It is contraindicated in patients with aortic regurgitation, aortic dissection, or severe peripheral artery disease. The major complications are vascular and thrombotic. Intravenous heparin is given in order to reduce thrombotic complications.

Another potentially useful tool is the Impella device (Abiomed, Danvers, Massachusetts). The catheter is placed percutaneously from the femoral artery into the left ventricle. The catheter has a small micro-axial pump at its tip that can pump up to 2.5–5 L/min from the left ventricle to the aorta. Other support devices include TandemHeart (CardiacAssist, Pittsburgh, Pennsylvania), which involves placement of a large 21-French catheter from the femoral vein through the right atrium into the left atrium using the transseptal technique and a catheter in the femoral artery. A centrifugal pump can deliver 5 L of blood per minute. It may be useful in patients in shock or with STEMI or very-high-risk PCI. Patients can also be placed on peripheral extracorporeal membrane oxygenation using large cannulas placed in the femoral artery and vein.

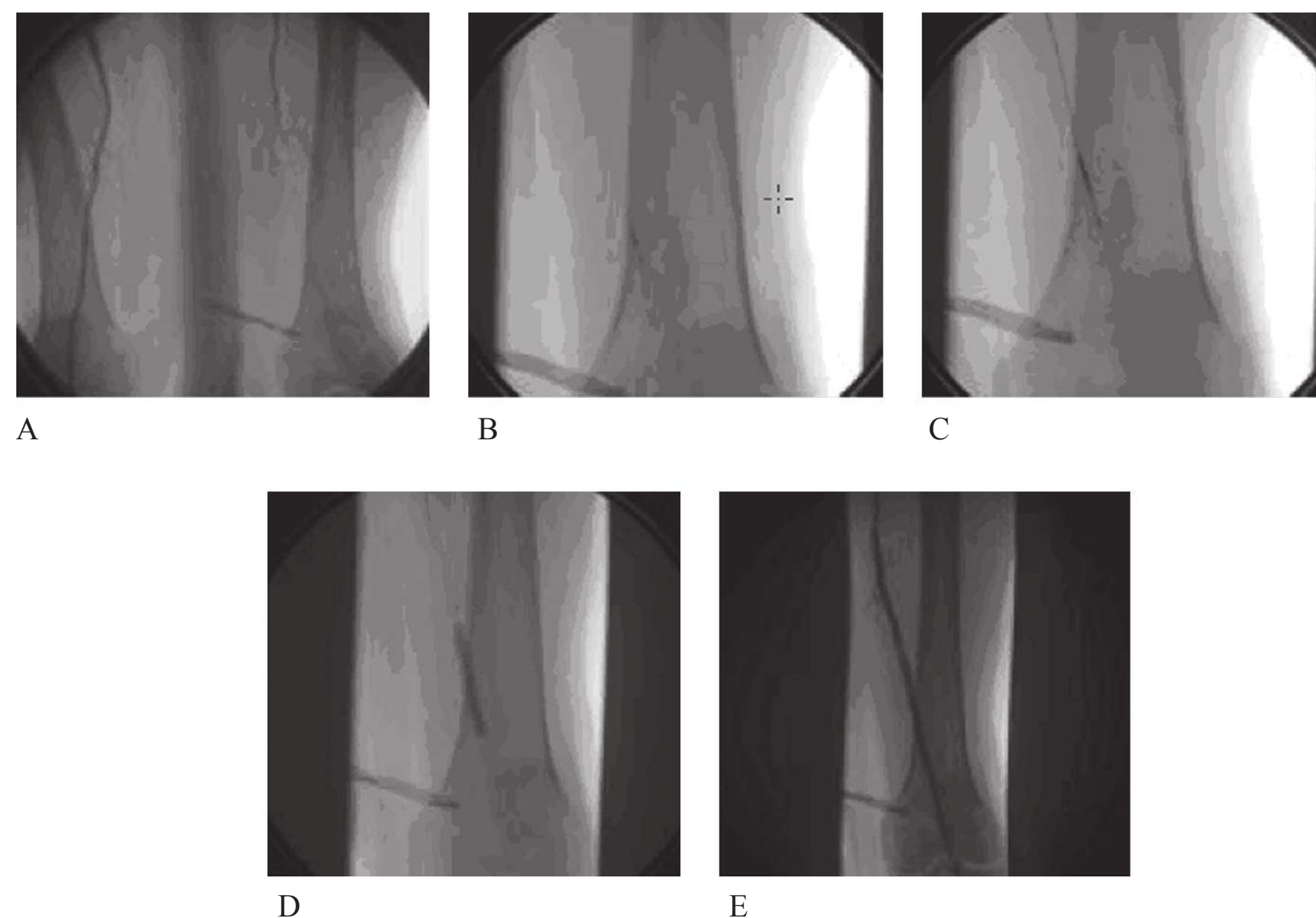


FIGURE 42-6

Peripheral interventional procedures have become highly effective at treating anatomic lesions previously amenable only to bypass surgery. A. Complete occlusion of the left superficial femoral artery. B. Wire and catheter advanced into subintimal space. C. Intravascular ultrasound positioned in the subintimal

space to guide retrograde wire placement through the occluded vessel. D. Balloon dilation of the occlusion. E. Stent placement with excellent angiographic result. (From A Al Mahameed, DL Bhatt: *Cleve Clin J Med* 73:S45, 2006; with permission.)

INTERVENTIONS FOR PULMONARY EMBOLISM

The treatment of deep vein thrombosis is intravenous anticoagulation, with placement of an inferior vena cava filter if recurrent pulmonary emboli occur. Postphlebitic syndrome is a serious condition due to chronic venous obstruction that can lead to chronic leg edema and venous ulcers. Preliminary studies suggest that mechanical treatments may have a role in treatment, and a large trial is ongoing.

Pulmonary emboli (PE) should be treated with fibrinolytic agents if massive and in some cases if submassive. Surgical pulmonary embolectomy is an option for the treatment of massive PE with hemodynamic instability in patients who have contraindications for systemic fibrinolysis or those in whom it has failed. Catheter-based therapies for submassive and massive PEs are still evolving, but studies have shown promise. The techniques employed include the use of aspiration of the clot with a large catheter (10 French), intraclot infusion of a thrombolytic agent followed by aspiration, ultrasound-assisted catheter-directed thrombolysis, and use of rheolytic thrombectomy. Success for these techniques has been reported to be 80–90%, with major complications occurring in 2–4% of patients.

INTERVENTIONS FOR REFRACTORY HYPERTENSION

The recent recognition of the importance of the renal sympathetic nerves in modulating blood pressure has led to a technique to selectively denervate renal

sympathetic nerves in patients with refractory hypertension. The procedure involves applying low-power radiofrequency treatment via a catheter along the length of both renal arteries. In the randomized Symplicity HTN-2 trial, renal denervation significantly reduced blood pressure compared with medical therapy. The Symplicity device (Medtronic) is approved in Europe, though the randomized and blinded U.S. Symplicity HTN-3 trial showed no effect.

CONCLUSION

Interventional cardiology continues to expand its borders. Treatment for coronary artery disease, including complex anatomic subsets, continues to advance, encroaching on what has traditionally been treated by CABG. Technological advances such as drug-eluting stents, now already in their second generation, and manual thrombus aspiration devices are improving the results of PCI. In particular, PCI has been shown to prevent future ischemic events in acute coronary syndromes. For patients with stable coronary disease, PCI has an important role in symptom alleviation. Treatment of peripheral and cerebrovascular disease has also benefited from the application of percutaneous techniques. Structural heart disease is increasingly being treated with percutaneous options, with a high likelihood that interventional approaches will compete with open-heart surgery in a significant proportion of cases in years to come.

CHAPTER 43

HYPERTENSIVE VASCULAR DISEASE



Theodore A. Kotchen

Hypertension is one of the leading causes of the global burden of disease. Approximately 7.6 million deaths (13–15% of the total) and 92 million disability-adjusted life years worldwide were attributable to high blood pressure in 2001. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. It often is associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of risk factors. Although antihypertensive therapy reduces the risks of cardiovascular and renal disease, large segments of the hypertensive population are either untreated or inadequately treated.

EPIDEMIOLOGY

Blood pressure levels, the rate of age-related increases in blood pressure, and the prevalence of hypertension vary among countries and among subpopulations within a country. Hypertension is present in all populations except for a small number of individuals living in developing countries. In industrialized societies, blood pressure increases steadily during the first two decades of life. In children and adolescents, blood pressure is associated with growth and maturation. Blood pressure “tracks” over time in children and between adolescence and young adulthood. In the United States, average systolic blood pressure is higher for men than for women during early adulthood, although among older individuals the age-related rate of rise is steeper for women. Consequently, among individuals age 60 and older, systolic blood pressures of women are higher than those of men. Among adults, diastolic blood pressure also increases progressively with age until ~55 years, after which it tends to decrease. The consequence is

a widening of pulse pressure (the difference between systolic and diastolic blood pressure) beyond age 60.

In the United States, based on results of the National Health and Nutrition Examination Survey (NHANES), approximately 30% (age-adjusted prevalence) of adults, or at least 65 million individuals, have hypertension (defined as any one of the following: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, taking antihypertensive medications). Hypertension prevalence is 33.5% in non-Hispanic blacks, 28.9% in non-Hispanic whites, and 20.7% in Mexican Americans. The likelihood of hypertension increases with age, and among individuals age ≥ 60 , the prevalence is 65.4%. Recent evidence suggests that the prevalence of hypertension in the United States may be increasing, possibly as a consequence of increasing obesity. The prevalence of hypertension and stroke mortality rates are higher in the southeastern United States than in other regions. In African Americans, hypertension appears earlier, is generally more severe, and results in higher rates of morbidity and mortality from stroke, left ventricular hypertrophy, CHF, and end-stage renal disease (ESRD) than in white Americans.

Both environmental and genetic factors may contribute to regional and racial variations in hypertension prevalence. Studies of societies undergoing “acculturation” and studies of migrants from a less to a more urbanized setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong, independent risk factors for hypertension. It has been estimated that 60% of hypertensives are $>20\%$ overweight. Among populations, hypertension prevalence is related to dietary NaCl intake, and the age-related increase in blood pressure may be augmented by a high NaCl intake. Low dietary intakes of calcium and potassium also may contribute to the risk of hypertension. The urine sodium-to-potassium ratio (an index of both sodium and potassium intakes) is a stronger

correlate of blood pressure than is either sodium or potassium alone. Alcohol consumption, psychosocial stress, and low levels of physical activity also may contribute to hypertension.

Adoption, twin, and family studies document a significant heritable component to blood pressure levels and hypertension. Family studies controlling for a common environment indicate that blood pressure heritabilities are in the range 15–35%. In twin studies, heritability estimates of blood pressure are ~60% for males and 30–40% for females. High blood pressure before age 55 occurs 3.8 times more frequently among persons with a positive family history of hypertension. However, to date, only a fraction of high heritability estimates are accounted for by specific genetic determinants.

GENETIC CONSIDERATIONS



Although specific genetic variants have been identified in rare Mendelian forms of hypertension (**Table 43–5**), these variants are not applicable to the vast majority (>98%) of patients with hypertension. For most individuals, it is likely that hypertension represents a polygenic disorder in which a combination of genes acts in concert with environmental exposures to make only a modest contribution to blood pressure. Further, different subsets of genes may lead to different phenotypes associated with hypertension, e.g., obesity, dyslipidemia, insulin resistance.

Several strategies are being used in the search for specific hypertension-related genes. Animal models (including selectively bred rats and congenic rat strains) provide a powerful approach for evaluating genetic loci and genes associated with hypertension. Comparative mapping strategies allow for the identification of syntenic genomic regions between the rat and human genomes that may be involved in blood pressure regulation. In association studies, different alleles (or combinations of alleles at different loci) of specific candidate genes or chromosomal regions are compared in hypertensive patients and normotensive control subjects. Current evidence suggests that genes that encode components of the renin-angiotensin-aldosterone system, along with angiotensinogen and angiotensin-converting enzyme (ACE) polymorphisms, may be related to hypertension and to blood pressure sensitivity to dietary NaCl. The α -adducin gene is thought to be associated with increased renal tubular absorption of sodium, and variants of this gene may be associated with hypertension and salt sensitivity of blood pressure. Other genes possibly related to hypertension include genes encoding the AT_1 receptor, aldosterone synthase, atrial natriuretic peptide, and the β_2 adrenoreceptor. Genomewide association studies involve rapidly scanning markers across the entire genome to identify loci (not specific genes) associated with an observable

trait (e.g., blood pressure) or a particular disease. This strategy has been facilitated by the availability of dense genotyping chips and the International HapMap. Results of candidate gene studies often have not been replicated, and in contrast to several other polygenic disorders, genomewide association studies have had limited success in identifying genetic determinants of hypertension.

Preliminary evidence suggests that there may also be genetic determinants of target organ damage attributed to hypertension. Family studies indicate significant heritability of left ventricular mass, and there is considerable individual variation in the responses of the heart to hypertension. Family studies and variations in candidate genes associated with renal damage suggest that genetic factors also may contribute to hypertensive nephropathy. Specific genetic variants have been linked to CHD and stroke.

In the future, it is possible that DNA analysis will predict individual risk for hypertension and target organ damage and will identify responders to specific classes of antihypertensive agents. However, with the exception of the rare, monogenic hypertensive diseases, the genetic variants associated with hypertension remain to be confirmed, and the intermediate steps by which these variants affect blood pressure remain to be determined.

MECHANISMS OF HYPERTENSION

To provide a framework for understanding the pathogenesis of and treatment options for hypertensive disorders, it is useful to understand factors involved in the regulation of both normal and elevated arterial pressure. Cardiac output and peripheral resistance are the two determinants of arterial pressure (**Fig. 43-1**). Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries (lumen diameter 100–400 μ m) and arterioles.

INTRAVASCULAR VOLUME

Sodium is predominantly an extracellular ion and is a primary determinant of the extracellular fluid volume. When NaCl intake exceeds the capacity of the kidney to

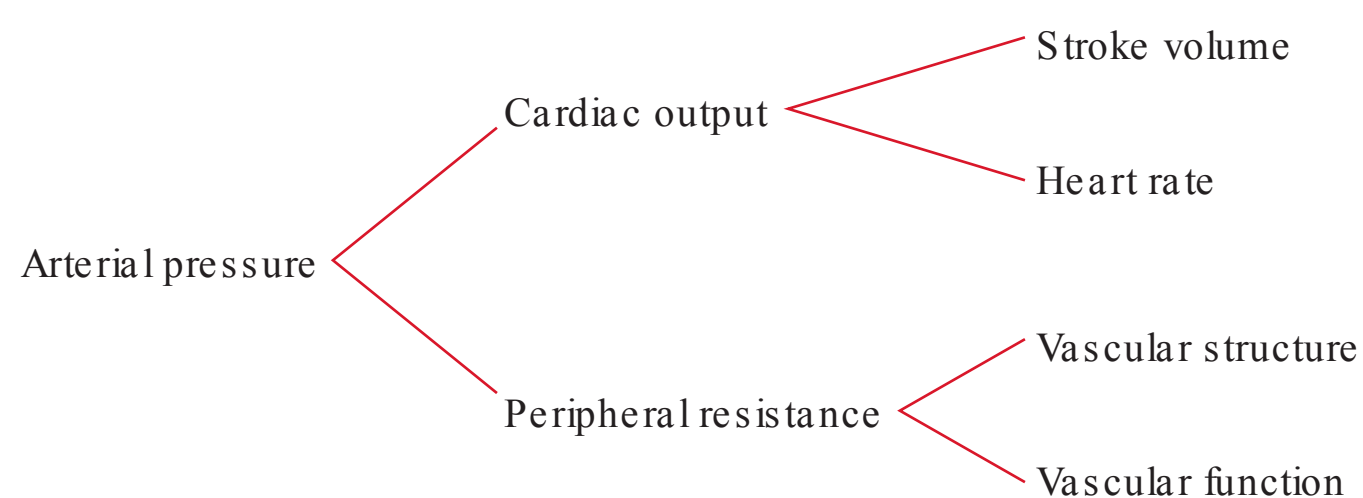


FIGURE 43-1
Determinants of arterial pressure.

excrete sodium, vascular volume may initially expand and cardiac output may increase. However, many vascular beds have the capacity to autoregulate blood flow, and if constant blood flow is to be maintained in the face of increased arterial pressure, resistance within that bed must increase, since

$$\text{Blood flow} = \frac{\text{pressure across the avascular bed}}{\text{vascular resistance}}$$

The initial elevation of blood pressure in response to vascular volume expansion may be related to an increase of cardiac output; however, over time, peripheral resistance increases and cardiac output reverts toward normal. Whether this hypothesized sequence of events occurs in the pathogenesis of hypertension is not clear. What is clear is that salt can activate a number of neural, endocrine/paracrine, and vascular mechanisms, all of which have the potential to increase arterial pressure. The effect of sodium on blood pressure is related to the provision of sodium with chloride; nonchloride salts of sodium have little or no effect on blood pressure. As arterial pressure increases in response to a high NaCl intake, urinary sodium excretion increases and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this “pressure-natriuresis” phenomenon may involve a subtle increase in the glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pressure are required to achieve natriuresis and sodium balance.

NaCl-dependent hypertension may be a consequence of a decreased capacity of the kidney to excrete sodium, due either to intrinsic renal disease or to increased production of a salt-retaining hormone (mineralocorticoid) resulting in increased renal tubular reabsorption of sodium. Renal tubular sodium reabsorption also may be augmented by increased neural activity to the kidney. In each of these situations, a higher arterial pressure may be required to achieve sodium balance. Conversely, salt-wasting disorders are associated with low blood pressure levels. ESRD is an extreme example of volume-dependent hypertension. In ~80% of these patients, vascular volume and hypertension can be controlled with adequate dialysis; in the other 20%, the mechanism of hypertension is related to increased activity of the renin-angiotensin system and is likely to be responsive to pharmacologic blockade of renin-angiotensin.

AUTONOMIC NERVOUS SYSTEM

Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the

long-term regulation of arterial pressure. Norepinephrine, epinephrine, and dopamine all play important roles in tonic and phasic cardiovascular regulation.

The activities of the adrenergic receptors are mediated by guanosine nucleotide-binding regulatory proteins (G proteins) and by intracellular concentrations of downstream second messengers. In addition to receptor affinity and density, physiologic responsiveness to catecholamines may be altered by the efficiency of receptor-effector coupling at a site “distal” to receptor binding. The receptor sites are relatively specific both for the transmitter substance and for the response that occupancy of the receptor site elicits. Based on their physiology and pharmacology, adrenergic receptors have been divided into two principal types: α and β . These types have been differentiated further into α_1 , α_2 , β_1 , and β_2 receptors. Recent molecular cloning studies have identified several additional subtypes. α Receptors are occupied and activated more avidly by norepinephrine than by epinephrine, and the reverse is true for β receptors. α_1 Receptors are located on postsynaptic cells in smooth muscle and elicit vasoconstriction. α_2 Receptors are localized on presynaptic membranes of postganglionic nerve terminals that synthesize norepinephrine. When activated by catecholamines, α_2 receptors act as negative feedback controllers, inhibiting further norepinephrine release. In the kidney, activation of α_1 -adrenergic receptors increases renal tubular reabsorption of sodium. Different classes of antihypertensive agents either inhibit α_1 receptors or act as agonists of α_2 receptors and reduce systemic sympathetic outflow. Activation of myocardial β_1 receptors stimulates the rate and strength of cardiac contraction and consequently increases cardiac output. β_1 Receptor activation also stimulates renin release from the kidney. Another class of antihypertensive agents acts by inhibiting β_1 receptors. Activation of β_2 receptors by epinephrine relaxes vascular smooth muscle and results in vasodilation.

Circulating catecholamine concentrations may affect the number of adrenoreceptors in various tissues. Downregulation of receptors may be a consequence of sustained high levels of catecholamines and provides an explanation for decreasing responsiveness, or tachyphylaxis, to catecholamines. For example, orthostatic hypotension frequently is observed in patients with pheochromocytoma, possibly due to the lack of norepinephrine-induced vasoconstriction with assumption of the upright posture. Conversely, with chronic reduction of neurotransmitter substances, adrenoreceptors may increase in number or be upregulated, resulting in increased responsiveness to the neurotransmitter. Chronic administration of agents that block adrenergic receptors may result in upregulation, and abrupt withdrawal of those agents may produce a condition of temporary hypersensitivity to sympathetic stimuli. For

example, clonidine is an antihypertensive agent that is a centrally acting α_2 agonist that inhibits sympathetic outflow. Rebound hypertension may occur with the abrupt cessation of clonidine therapy, probably as a consequence of upregulation of α_1 receptors.

Several reflexes modulate blood pressure on a minute-to-minute basis. One arterial baroreflex is mediated by stretch-sensitive sensory nerve endings in the carotid sinuses and the aortic arch. The rate of firing of these baroreceptors increases with arterial pressure, and the net effect is a decrease in sympathetic outflow, resulting in decreases in arterial pressure and heart rate. This is a primary mechanism for rapid buffering of acute fluctuations of arterial pressure that may occur during postural changes, behavioral or physiologic stress, and changes in blood volume. However, the activity of the baroreflex declines or adapts to sustained increases in arterial pressure such that the baroreceptors are reset to higher pressures. Patients with autonomic neuropathy and impaired baroreflex function may have extremely labile blood pressures with difficult-to-control episodic blood pressure spikes associated with tachycardia.

In both normal-weight and obese individuals, hypertension often is associated with increased sympathetic outflow. Based on recordings of postganglionic muscle nerve activity (detected by a microelectrode inserted in a peroneal nerve in the leg), sympathetic outflow tends to be higher in hypertensive than in normotensive individuals. Sympathetic outflow is increased in obesity-related hypertension and in hypertension associated with obstructive sleep apnea. Baroreceptor activation via electrical stimulation of carotid sinus afferent nerves lowers blood pressure in patients with “resistant” hypertension. Drugs that block the sympathetic nervous system are potent antihypertensive agents, indicating that the sympathetic nervous system plays a permissive, although not necessarily a causative, role in the maintenance of increased arterial pressure.

Pheochromocytoma is the most blatant example of hypertension related to increased catecholamine production, in this instance by a tumor. Blood pressure can be reduced by surgical excision of the tumor or by pharmacologic treatment with an α_1 receptor antagonist or with an inhibitor of tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis.

RENIN-ANGIOTENSIN-ALDOSTERONE

The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. Renin is an aspartyl protease that is synthesized as an enzymatically inactive precursor, prorenin. Most renin in

the circulation is synthesized in the renal afferent renal arteriole. Prorenin may be secreted directly into the circulation or may be activated within secretory cells and released as active renin. Although human plasma contains two to five times more prorenin than renin, there is no evidence that prorenin contributes to the physiologic activity of this system. There are three primary stimuli for renin secretion: (1) decreased NaCl transport in the distal portion of the thick ascending limb of the loop of Henle that abuts the corresponding afferent arteriole (macula densa), (2) decreased pressure or stretch within the renal afferent arteriole (baroreceptor mechanism), and (3) sympathetic nervous system stimulation of renin-secreting cells via β_1 adrenoreceptors. Conversely, renin secretion is inhibited by increased NaCl transport in the thick ascending limb of the loop of Henle, by increased stretch within the renal afferent arteriole, and by β_1 receptor blockade. In addition, angiotensin II directly inhibits renin secretion due to angiotensin II type 1 receptors on juxtaglomerular cells, and renin secretion increases in response to pharmacologic blockade of either ACE or angiotensin II receptors.

Once released into the circulation, active renin cleaves a substrate, angiotensinogen, to form an inactive decapeptide, angiotensin I (Fig. 43-2). A converting enzyme, located primarily but not exclusively in the pulmonary circulation, converts angiotensin I to the active octapeptide, angiotensin II, by releasing the C-terminal histidyl-leucine dipeptide. The same

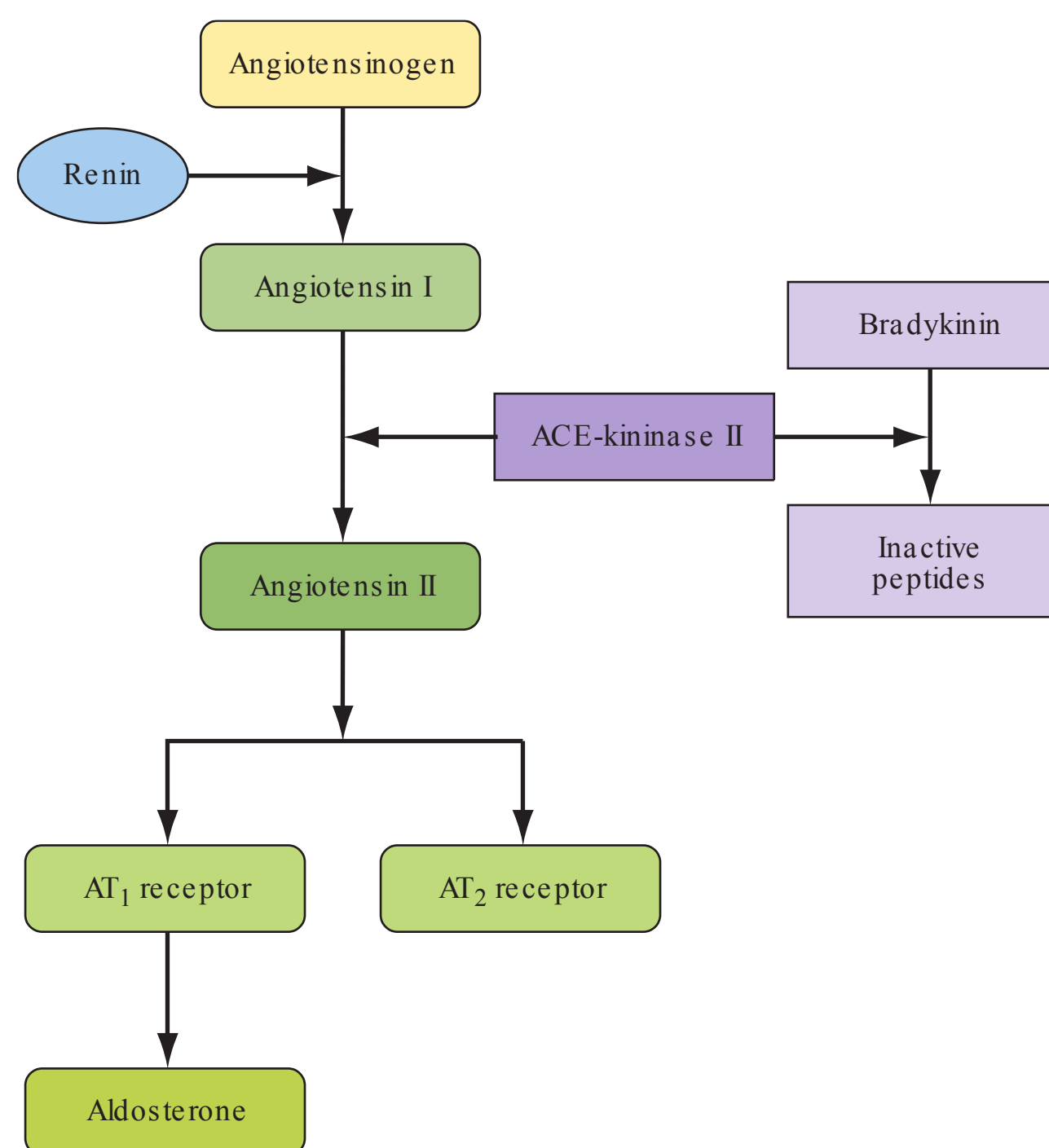


FIGURE 43-2

Renin-angiotensin-aldosterone axis. ACE, angiotensin-converting enzyme.

converting enzyme cleaves a number of other peptides, including and thereby inactivating the vasodilator bradykinin. Acting primarily through angiotensin II type 1 (AT₁) receptors on cell membranes, angiotensin II is a potent pressor substance, the primary tropic factor for the secretion of aldosterone by the adrenal zona glomerulosa, and a potent mitogen that stimulates vascular smooth muscle cell and myocyte growth. Independent of its hemodynamic effects, angiotensin II may play a role in the pathogenesis of atherosclerosis through a direct cellular action on the vessel wall. The angiotensin II type 2 (AT₂) receptor has the opposite functional effects of the AT₁ receptor. The AT₂ receptor induces vasodilation, sodium excretion, and inhibition of cell growth and matrix formation. Experimental evidence suggests that the AT₂ receptor improves vascular remodeling by stimulating smooth muscle cell apoptosis and contributes to the regulation of glomerular filtration rate. AT₁ receptor blockade induces an increase in AT₂ receptor activity.

Renin-secreting tumors are clear examples of renin-dependent hypertension. In the kidney, these tumors include benign hemangiopericytomas of the juxtaglomerular apparatus and, infrequently, renal carcinomas, including Wilms' tumors. Renin-producing carcinomas also have been described in lung, liver, pancreas, colon, and adrenals. In these instances, in addition to excision and/or ablation of the tumor, treatment of hypertension includes pharmacologic therapies targeted to inhibit angiotensin II production or action. Renovascular hypertension is another renin-mediated form of hypertension. Obstruction of the renal artery leads to decreased renal perfusion pressure, thereby stimulating renin secretion. Over time, possibly as a consequence of secondary renal damage, this form of hypertension may become less renin dependent.

Angiotensinogen, renin, and angiotensin II are also synthesized locally in many tissues, including the brain, pituitary, aorta, arteries, heart, adrenal glands, kidneys, adipocytes, leukocytes, ovaries, testes, uterus, spleen, and skin. Angiotensin II in tissues may be formed by the enzymatic activity of renin or by other proteases, e.g., tonin, chymase, and cathepsins. In addition to regulating local blood flow, tissue angiotensin II is a mitogen that stimulates growth and contributes to modeling and repair. Excess tissue angiotensin II may contribute to atherosclerosis, cardiac hypertrophy, and renal failure and consequently may be a target for pharmacologic therapy to prevent target organ damage.

Angiotensin II is the primary tropic factor regulating the synthesis and secretion of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone synthesis is also dependent on potassium, and aldosterone secretion may be decreased in potassium-depleted individuals. Although acute elevations of

adrenocorticotrophic hormone (ACTH) levels also increase aldosterone secretion, ACTH is not an important tropic factor for the chronic regulation of aldosterone.

Aldosterone is a potent mineralocorticoid that increases sodium reabsorption by amiloride-sensitive epithelial sodium channels (ENaC) on the apical surface of the principal cells of the renal cortical collecting duct. Electric neutrality is maintained by exchanging sodium for potassium and hydrogen ions. Consequently, increased aldosterone secretion may result in hypokalemia and alkalosis.

Cortisol also binds to the mineralocorticoid receptor but normally functions as a less potent mineralocorticoid than aldosterone because cortisol is converted to cortisone by the enzyme 11 β -hydroxysteroid dehydrogenase type 2. Cortisone has no affinity for the mineralocorticoid receptor. Primary aldosteronism is a compelling example of mineralocorticoid-mediated hypertension. In this disorder, adrenal aldosterone synthesis and release are independent of renin-angiotensin, and renin release is suppressed by the resulting volume expansion.

Mineralocorticoid receptors are expressed in a number of tissues in addition to the kidney, and mineralocorticoid receptor activation induces structural and functional alterations in the heart, kidney, and blood vessels, leading to myocardial fibrosis, nephrosclerosis, and vascular inflammation and remodeling, perhaps as a consequence of oxidative stress. These effects are amplified by a high salt intake. In animal models, high circulating aldosterone levels stimulate cardiac fibrosis and left ventricular hypertrophy, and spironolactone (an aldosterone antagonist) prevents aldosterone-induced myocardial fibrosis. Pathologic patterns of left ventricular geometry also have been associated with elevations of plasma aldosterone concentration in hypertensive patients. In patients with CHF, low-dose spironolactone reduces the risk of progressive heart failure and sudden death from cardiac causes by 30%. Due to a renal hemodynamic effect, in patients with primary aldosteronism, high circulating levels of aldosterone also may cause glomerular hyperfiltration and albuminuria. These renal effects are reversible after removal of the effects of excess aldosterone by adrenalectomy or spironolactone.

Increased activity of the renin-angiotensin-aldosterone axis is not invariably associated with hypertension. In response to a low-NaCl diet or to volume contraction, arterial pressure and volume homeostasis may be maintained by increased activity of the renin-angiotensin-aldosterone axis. Secondary aldosteronism (i.e., increased aldosterone secondary to increased renin-angiotensin), but not hypertension, also is observed in edematous states such as CHF and liver disease.

Vascular radius and compliance of resistance arteries are important determinants of arterial pressure. Resistance to flow varies inversely with the fourth power of the radius, and consequently, small decreases in lumen size significantly increase resistance. In hypertensive patients, structural, mechanical, or functional changes may reduce the lumen diameter of small arteries and arterioles. Remodeling refers to geometric alterations in the vessel wall without a change in vessel volume. Hypertrophic (increased cell size, and increased deposition of intercellular matrix) or eutrophic vascular remodeling results in decreased lumen size and, hence, increased peripheral resistance. Apoptosis, low-grade inflammation, and vascular fibrosis also contribute to remodeling. Lumen diameter also is related to elasticity of the vessel. Vessels with a high degree of elasticity can accommodate an increase of volume with relatively little change in pressure, whereas in a semirigid vascular system, a small increment in volume induces a relatively large increment of pressure.

Hypertensive patients may have stiffer arteries due to arteriosclerosis, and high systolic blood pressures and wide pulse pressures are a consequence of decreased vascular compliance. Due to arterial stiffness, central blood pressures (aortic, carotid) may not correspond to brachial artery pressures. Ejection of blood into the aorta elicits a pressure wave that is propagated at a given velocity. The forward travelling wave generates a reflected wave that travels backward toward the ascending aorta. Although mean arterial pressure is determined by cardiac output and peripheral resistance, pulse pressure is related to the functional properties of large arteries and the amplitude and timing of the incident and reflected waves. Increased arterial stiffness results in increased pulse wave velocity of both incident and reflected waves. Due to the timing of these waves, the consequence is augmentation of aortic systolic pressure and a reduction of aortic diastolic pressure, i.e., an increase in pulse pressure. The aortic augmentation index, an index of arterial stiffening, is calculated as the ratio of central arterial pressure-to-pulse pressure. Central blood pressure may be measured directly by placing a sensor in the aorta or noninvasively by radial tonometry using commercially available devices. Central blood pressure and the aortic augmentation index are strong, independent predictors of cardiovascular disease and all-cause mortality.

Ion transport by vascular smooth muscle cells may contribute to hypertension-associated abnormalities of vascular tone and vascular growth, both of which are modulated by intracellular pH (pH_i). Three ion transport mechanisms participate in the regulation of pH_i : (1) $\text{Na}^+\text{-H}^+$ exchange, (2) Na^+ -dependent $\text{HCO}_3^- \text{-Cl}^-$ exchange, and (3) cation-independent

$\text{HCO}_3^- \text{-Cl}^-$ exchange. Based on measurements in cell types that are more accessible than vascular smooth muscle (e.g., leukocytes, erythrocytes, platelets, skeletal muscle), activity of the $\text{Na}^+\text{-H}^+$ exchanger is increased in hypertension, and this may result in increased vascular tone by two mechanisms. First, increased sodium entry may lead to increased vascular tone by activating $\text{Na}^+\text{-Ca}^{2+}$ exchange and thereby increasing intracellular calcium. Second, increased pH_i enhances calcium sensitivity of the contractile apparatus, leading to an increase in contractility for a given intracellular calcium concentration. Additionally, increased $\text{Na}^+\text{-H}^+$ exchange may stimulate growth of vascular smooth muscle cells by enhancing sensitivity to mitogens.

Vascular endothelial function also modulates vascular tone. The vascular endothelium synthesizes and releases several vasoactive substances, including nitric oxide, a potent vasodilator. Endothelium-dependent vasodilation is impaired in hypertensive patients. This impairment often is assessed with high-resolution ultrasonography before and after the hyperemic phase of reperfusion that follows 5 minutes of forearm ischemia. Alternatively, endothelium-dependent vasodilation may be assessed in response to an intra-arterially infused endothelium-dependent vasodilator, e.g., acetylcholine. Endothelin is a vasoconstrictor peptide produced by the endothelium, and orally active endothelin antagonists may lower blood pressure in patients with resistant hypertension.

Currently, it is not known if the hypertension-related vascular abnormalities of ion transport and endothelial function are primary alterations or secondary consequences of elevated arterial pressure. Limited evidence suggests that vascular compliance and endothelium-dependent vasodilation may be improved by aerobic exercise, weight loss, and antihypertensive agents. It remains to be determined whether these interventions affect arterial structure and stiffness via a blood pressure-independent mechanism and whether different classes of antihypertensive agents preferentially affect vascular structure and function.

PATHOLOGIC CONSEQUENCES OF HYPERTENSION

Hypertension is an independent predisposing factor for heart failure, coronary artery disease, stroke, renal disease, and peripheral arterial disease (PAD).

HEART

Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations

leading to left ventricular hypertrophy, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias.

Individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death. Aggressive control of hypertension can regress or reverse left ventricular hypertrophy and reduce the risk of cardiovascular disease. It is not clear whether different classes of antihypertensive agents have an added impact on reducing left ventricular mass, independent of their blood pressure–lowering effect.

CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two. Abnormalities of diastolic function that range from asymptomatic heart disease to overt heart failure are common in hypertensive patients. Approximately one-third of patients with CHF have normal systolic function but abnormal diastolic function. Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia. Cardiac catheterization provides the most accurate assessment of diastolic function. Alternatively, diastolic function can be evaluated by several noninvasive methods, including echocardiography and radionuclide angiography.

BRAIN

Stroke is the second most frequent cause of death in the world; it accounts for 5 million deaths each year, with an additional 15 million persons having nonfatal strokes. Elevated blood pressure is the strongest risk factor for stroke. Approximately 85% of strokes are due to infarction, and the remainder are due to either intracerebral or subarachnoid hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years. Treatment of hypertension decreases the incidence of both ischemic and hemorrhagic strokes.

Hypertension also is associated with impaired cognition in an aging population, and longitudinal studies support an association between midlife hypertension and late-life cognitive decline. Hypertension-related cognitive impairment and dementia may be a consequence of a single infarct due to occlusion of a “strategic” larger vessel or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia. Several clinical trials suggest that antihypertensive therapy has a beneficial effect on cognitive function, although this remains an active area of investigation.

Cerebral blood flow remains unchanged over a wide range of arterial pressures (mean arterial pressure of 50–150 mmHg) through a process termed

autoregulation of blood flow. In patients with the clinical syndrome of malignant hypertension, encephalopathy is related to failure of autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion. Signs and symptoms of hypertensive encephalopathy may include severe headache, nausea and vomiting (often of a projectile nature), focal neurologic signs, and alterations in mental status. Untreated, hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours. It is important to distinguish hypertensive encephalopathy from other neurologic syndromes that may be associated with hypertension, e.g., cerebral ischemia, hemorrhagic or thrombotic stroke, seizure disorder, mass lesions, pseudotumor cerebri, delirium tremens, meningitis, acute intermittent porphyria, traumatic or chemical injury to the brain, and uremic encephalopathy.

KIDNEY

The kidney is both a target and a cause of hypertension. Primary renal disease is the most common etiology of secondary hypertension. Mechanisms of kidney-related hypertension include a diminished capacity to excrete sodium, excessive renin secretion in relation to volume status, and sympathetic nervous system overactivity. Conversely, hypertension is a risk factor for renal injury and ESRD. The increased risk associated with high blood pressure is graded, continuous, and present throughout the distribution of blood pressure above optimal pressure. Renal risk appears to be more closely related to systolic than to diastolic blood pressure, and black men are at greater risk than white men for developing ESRD at every level of blood pressure.

Atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular injury also may be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. Studies of hypertension-related renal damage, primarily in experimental animals, suggest that loss of autoregulation of renal blood flow at the afferent arteriole results in transmission of elevated pressures to an unprotected glomerulus with ensuing hyperfiltration, hypertrophy, and eventual focal segmental glomerular sclerosis. With progressive renal injury there is a loss of autoregulation of renal blood flow and glomerular filtration rate, resulting in a lower blood pressure threshold for renal damage and a steeper slope between blood pressure and renal damage. The result may be a vicious cycle of renal damage and nephron loss leading to more severe hypertension, glomerular hyperfiltration, and further renal damage. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may

504 also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in focal necrosis of the glomerular tuft.

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio >300 mg/g) or microalbuminuria (a random urine albumin/creatinine ratio 30–300 mg/g) are early markers of renal injury. These are also risk factors for renal disease progression and cardiovascular disease.

PERIPHERAL ARTERIES

In addition to contributing to the pathogenesis of hypertension, blood vessels are a target organ for atherosclerotic disease secondary to long-standing elevated blood pressure. In hypertensive patients, vascular disease is a major contributor to stroke, heart disease, and renal failure. Further, hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. Although patients with stenotic lesions of the lower extremities may be asymptomatic, intermittent claudication is the classic symptom of PAD. The ankle-brachial index is a useful approach for evaluating PAD and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood pressure. An ankle-brachial index <0.90 is considered diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel. An ankle-brachial index <0.80 is associated with elevated blood pressure, particularly systolic blood pressure.

DEFINING HYPERTENSION

From an epidemiologic perspective, there is no obvious level of blood pressure that defines hypertension. In adults, there is a continuous, incremental risk of cardiovascular disease, stroke, and renal disease across levels of both systolic and diastolic blood pressure. The Multiple Risk Factor Intervention Trial (MRFIT), which included >350,000 male participants, demonstrated a continuous and graded influence of both systolic and diastolic blood pressure on CHD mortality, extending down to systolic blood pressures of 120 mmHg. Similarly, results of a meta-analysis involving almost 1 million participants indicate that ischemic heart disease mortality, stroke mortality, and mortality from other vascular causes are directly related to the height of the blood pressure, beginning at 115/75 mmHg, without evidence of a threshold. Cardiovascular disease risk doubles for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic pressure. Among older

individuals, systolic blood pressure and pulse pressure are more powerful predictors of cardiovascular disease than is diastolic blood pressure.

Clinically, hypertension may be defined as that level of blood pressure at which the institution of therapy reduces blood pressure–related morbidity and mortality. Current clinical criteria for defining hypertension generally are based on the average of two or more seated blood pressure readings during each of two or more outpatient visits. A recent classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is frequent among the elderly (Table 43-1). In children and adolescents, hypertension generally is defined as systolic and/or diastolic blood pressure consistently >95th percentile for age, sex, and height. Blood pressures between the 90th and 95th percentiles are considered prehypertensive and are an indication for lifestyle interventions.

Home blood pressure and average 24-h ambulatory blood pressure measurements are generally lower than clinic blood pressures. Because ambulatory blood pressure recordings yield multiple readings throughout the day and night, they provide a more comprehensive assessment of the vascular burden of hypertension than do a limited number of office readings. Increasing evidence suggests that home blood pressures, including 24-h blood pressure recordings, more reliably predict target organ damage than do office blood pressures. Blood pressure tends to be higher in the early morning hours, soon after waking, than at other times of day. Myocardial infarction and stroke are more common in the early morning hours. Nighttime blood pressures are generally 10–20% lower than daytime blood pressures, and an attenuated nighttime blood pressure “dip” may be associated with increased cardiovascular disease risk. Recommended criteria for a diagnosis of hypertension, based on 24-h blood pressure monitoring, are average

TABLE 43-1

BLOOD PRESSURE CLASSIFICATION		
BLOOD PRESSURE CLASSIFICATION	SYSTOLIC, MMHG	DIASTOLIC, MMHG
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	≥160	or ≥100
Isolated systolic hypertension	≥140	and <90

Source: Adapted from AVChobanian et al: JAMA 289:2560, 2003.

awake blood pressure $\geq 135/85$ mmHg and asleep blood pressure $\geq 120/75$ mmHg. These levels approximate a clinic blood pressure of 140/90 mmHg.

Approximately 15–20% of patients with stage 1 hypertension (as defined in Table 43-1) based on office blood pressures have average ambulatory readings $<135/85$ mmHg. This phenomenon, so-called white coat hypertension, also may be associated with an increased risk of target organ damage, although to a lesser extent than in individuals with elevated office and ambulatory readings. Individuals with white coat hypertension are also at increased risk for developing sustained hypertension.

CLINICAL DISORDERS OF HYPERTENSION

Depending on methods of patient ascertainment, ~80–95% of hypertensive patients are diagnosed as having primary, or “essential,” hypertension. In the remaining 5–20% of hypertensive patients, a specific underlying disorder causing the elevation of blood pressure can be identified (**Tables 43-2 and 43-3**). In individuals with “secondary” hypertension, a specific mechanism for the blood pressure elevation is often more apparent.

PRIMARY HYPERTENSION

Primary hypertension tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors. The prevalence of primary hypertension increases with age, and individuals with relatively high blood pressures at younger ages are at increased risk for the subsequent development of hypertension. It is likely that primary hypertension represents a spectrum of disorders with different underlying pathophysiologies. In the majority of patients with established hypertension, peripheral resistance is increased and cardiac output is normal or decreased; however, in younger patients with mild or labile hypertension, cardiac output may be increased and peripheral resistance may be normal.

TABLE 43-2

SYSTOLIC HYPERTENSION WITH WIDE PULSE PRESSURE
1. Decreased vascular compliance (arteriosclerosis) 2. Increased cardiac output a. Aortic regurgitation b. Thyrotoxicosis c. Hyperkinetic heart syndrome d. Fever e. Arteriovenous fistula f. Patent ductus arteriosus

TABLE 43-3

SECONDARY CAUSES OF SYSTOLIC AND DIASTOLIC HYPERTENSION	
Renal	Parenchymal diseases, renal cysts (including polycystic kidney disease), renal tumors (including renin-secreting tumors), obstructive uropathy
Renovascular	Arteriosclerotic, fibromuscular dysplasia
Adrenal	Primary aldosteronism, Cushing's syndrome, 17 α -hydroxylase deficiency, 11 β -hydroxylase deficiency, 11-hydroxysteroid dehydrogenase deficiency (licorice), pheochromocytoma
Aortic coarctation	
Obstructive sleep apnea	
Preeclampsia/eclampsia	
Neurogenic	Psychogenic, diencephalic syndrome, familial dysautonomia, polyneuritis (acute porphyria, lead poisoning), acute increased intracranial pressure, acute spinal cord section
Miscellaneous endocrine	Hypothyroidism, hyperthyroidism, hypercalcemia, acromegaly
Medications	High-dose estrogens, adrenal steroids, decongestants, appetite suppressants, cyclosporine, tricyclic antidepressants, monoamine oxidase inhibitors, erythropoietin, nonsteroidal anti-inflammatory agents, cocaine
Mendelian forms of hypertension	See Table 43-4

When plasma renin activity (PRA) is plotted against 24-h sodium excretion, ~10–15% of hypertensive patients have high PRA and 25% have low PRA. High-renin patients may have a vasoconstrictor form of hypertension, whereas low-renin patients may have volume-dependent hypertension. Inconsistent associations between plasma aldosterone and blood pressure have been described in patients with primary hypertension. The association between aldosterone and blood pressure is more striking in African Americans, and PRA tends to be low in hypertensive African Americans. This raises the possibility that subtle increases in aldosterone may contribute to hypertension in at least some groups of patients who do not have overt primary aldosteronism. Furthermore, spironolactone, an aldosterone

TABLE 43-4

RARE MENDELIAN FORMS OF HYPERTENSION		
DISEASE	PHENOTYPE	GENETIC CAUSE
Glucocorticoid-remediable hyperaldosteronism	Autosomal dominant	Chimeric 11 β -hydroxylase/aldosterone gene on chromosome 8
	Absent or mild hypokalemia	
17 α -hydroxylase deficiency	Autosomal recessive	Random mutations of the CYP17 gene on chromosome 10
	Males: pseudohermaphroditism	
	Females: primary amenorrhea, absent secondary sexual characteristics	
11 β -hydroxylase deficiency	Autosomal recessive	Mutations of the CYP11B1 gene on chromosome 8q21-q22
	Masculinization	
11 β -hydroxysteroid dehydrogenase deficiency (apparent mineralocorticoid excess syndrome)	Autosomal recessive Hypokalemia, low renin, low aldosterone	Mutations in the 11 β -hydroxysteroid dehydrogenase gene
Liddle's syndrome	Autosomal dominant	Mutation subunits of the epithelial sodium channel SCNN1B and SCNN1C genes
	Hypokalemia, low renin, low aldosterone	
Pseudohypoaldosteronism type II (Gordon's syndrome)	Autosomal dominant	Linkage to chromosomes 1q31-q42 and 17p11-q21
	Hyperkalemia, normal glomerular filtration rate	
Hypertension exacerbated in pregnancy	Autosomal dominant	Missense mutation with substitution of leucine for serine at codon 810 (MR ₁₈₁₀)
	Severe hypertension in early pregnancy	
Polycystic kidney disease	Autosomal dominant	Mutations in the PKD1 gene on chromosome 16 and PKD2 gene on chromosome 4
	Large cystic kidneys, renal failure, liver cysts, cerebral aneurysms, valvular heart disease	
Pheochromocytoma	Autosomal dominant	
	(a) Multiple endocrine neoplasia, type 2A Medullary thyroid carcinoma, hyperparathyroidism	(a) Mutations in the RET protooncogene
	(b) Multiple endocrine neoplasia, type 2B Medullary thyroid carcinoma, mucosal neuro- mas, thickened corneal nerves, alimentary ganglioneuromatoses, marfanoid habitus	(b) Mutations in the RET protooncogene
	(c) von Hippel-Lindau disease Retinal angiomas, hemangioblastomas of the cerebellum and spinal cord, renal cell carcinoma	(c) Mutations in the VHL tumor-suppressor gene
	(d) Neurofibromatosis type 1 Multiple neurofibromas, café-au-lait spots	(d) Mutations in the NF1 tumor-suppressor gene

antagonist, may be a particularly effective antihypertensive agent for some patients with primary hypertension, including some patients with “drug-resistant” hypertension.

OBESITY AND THE METABOLIC SYNDROME

(See also Chap. 38) There is a well-documented association between obesity (body mass index >30 kg/m²)

and hypertension. Further, cross-sectional studies indicate a direct linear correlation between body weight (or body mass index) and blood pressure. Centrally located body fat is a more important determinant of blood pressure elevation than is peripheral body fat. In longitudinal studies, a direct correlation exists between change in weight and change in blood pressure over time. Sixty percent of hypertensive adults are more than 20% overweight. It has been established that 60–70% of

hypertension in adults may be directly attributable to adiposity.

Hypertension and dyslipidemia frequently occur together and in association with resistance to insulin-stimulated glucose uptake. The clustering of risk factors is often, but not invariably, associated with obesity, particularly abdominal obesity. Insulin resistance also is associated with an unfavorable imbalance in the endothelial production of mediators that regulate platelet aggregation, coagulation, fibrinolysis, and vessel tone. When these risk factors cluster, the risks for CHD, stroke, diabetes, and cardiovascular disease mortality are increased further.

Depending on the populations studied and the methodologies for defining insulin resistance, ~25–50% of nonobese, nondiabetic hypertensive persons are insulin resistant. The constellation of insulin resistance, abdominal obesity, hypertension, and dyslipidemia has been designated as the metabolic syndrome. As a group, first-degree relatives of patients with primary hypertension are also insulin resistant, and hyperinsulinemia (a surrogate marker of insulin resistance) may predict the eventual development of hypertension and cardiovascular disease. Although the metabolic syndrome may in part be heritable as a polygenic condition, the expression of the syndrome is modified by environmental factors, such as degree of physical activity and diet. Insulin sensitivity increases and blood pressure decreases in response to weight loss. The recognition that cardiovascular disease risk factors tend to cluster within individuals has important implications for the evaluation and treatment of hypertension. Evaluation of both hypertensive patients and individuals at risk for developing hypertension should include assessment of overall cardiovascular disease risk. Similarly, introduction of lifestyle modification strategies and drug therapies should address overall risk and not focus exclusively on hypertension.

RENAL PARENCHYMAL DISEASES

Virtually all disorders of the kidney may cause hypertension (Table 43-3), and renal disease is the most common cause of secondary hypertension. Hypertension is present in >80% of patients with chronic renal failure. In general, hypertension is more severe in glomerular diseases than in interstitial diseases such as chronic pyelonephritis. Conversely, hypertension may cause nephrosclerosis, and in some instances it may be difficult to determine whether hypertension or renal disease was the initial disorder. Proteinuria >1000 mg/d and an active urine sediment are indicative of primary renal disease. In either instance, the goals are to control blood pressure and retard the rate of progression of renal dysfunction.

RENOVASCULAR HYPERTENSION

Hypertension due to an occlusive lesion of a renal artery, renovascular hypertension, is a potentially curable form of hypertension. In the initial stages, the mechanism of hypertension generally is related to activation of the renin-angiotensin system. However, renin activity and other components of the renin-angiotensin system may be elevated only transiently; over time, recruitment of other pressure mechanisms may contribute to elevated arterial pressure. Two groups of patients are at risk for this disorder: older arteriosclerotic patients who have a plaque obstructing the renal artery, frequently at its origin, and patients with fibromuscular dysplasia. Atherosclerosis accounts for the large majority of patients with renovascular hypertension. Although fibromuscular dysplasia may occur at any age, it has a strong predilection for young white women. The prevalence in females is eightfold that in males. There are several histologic variants of fibromuscular dysplasia, including medial fibroplasia, perimedial fibroplasia, medial hyperplasia, and intimal fibroplasia. Medial fibroplasia is the most common variant and accounts for approximately two-thirds of patients. The lesions of fibromuscular dysplasia are frequently bilateral and, in contrast to atherosclerotic renovascular disease, tend to affect more distal portions of the renal artery.

Several clues from the history and physical examination may suggest renovascular hypertension. The diagnosis should be considered in patients with other evidence of atherosclerotic vascular disease. Although response to antihypertensive therapy does not exclude the diagnosis, severe or refractory hypertension, recent loss of hypertension control or recent onset of moderately severe hypertension, and unexplained deterioration of renal function or deterioration of renal function associated with an ACE inhibitor should raise the possibility of renovascular hypertension. Approximately 50% of patients with renovascular hypertension have an abdominal or flank bruit, and the bruit is more likely to be hemodynamically significant if it lateralizes or extends throughout systole into diastole.

If blood pressure is adequately controlled with a simple antihypertensive regimen and renal function remains stable, there may be little impetus to pursue an evaluation for renal artery stenosis, particularly in an older patient with atherosclerotic disease and comorbid conditions. Patients with long-standing hypertension, advanced renal insufficiency, or diabetes mellitus are less likely to benefit from renal vascular repair. The most effective medical therapies include an ACE inhibitor or an angiotensin II receptor blocker; however, these agents decrease glomerular filtration rate in a stenotic kidney owing to efferent renal arteriolar dilation. In the presence of bilateral renal artery stenosis or renal artery stenosis to a solitary kidney, progressive renal

insufficiency may result from the use of these agents. Importantly, the renal insufficiency is generally reversible after discontinuation of the offending drug.

If renal artery stenosis is suspected and if the clinical condition warrants an intervention such as percutaneous transluminal renal angioplasty (PTRA), placement of a vascular endoprosthesis (stent), or surgical renal revascularization, imaging studies should be the next step in the evaluation. As a screening test, renal blood flow may be evaluated with a radionuclide [^{131}I]-orthoiodohippurate (OIH) scan, or glomerular filtration rate may be evaluated with a [^{99}mTc]-diethylene-triamine pentaacetic acid (DTPA) scan before and after a single dose of captopril (or another ACE inhibitor). The following are consistent with a positive study: (1) decreased relative uptake by the involved kidney, which contributes <40% of total renal function, (2) delayed uptake on the affected side, and (3) delayed washout on the affected side. In patients with normal, or nearly normal, renal function, a normal captopril renogram essentially excludes functionally significant renal artery stenosis; however, its usefulness is limited in patients with renal insufficiency (creatinine clearance <20 mL/min) or bilateral renal artery stenosis. Additional imaging studies are indicated if the scan is positive. Doppler ultrasound of the renal arteries produces reliable estimates of renal blood flow velocity and offers the opportunity to track a lesion over time. Positive studies usually are confirmed at angiography, whereas false-negative results occur frequently, particularly in obese patients. Gadolinium-contrast magnetic resonance angiography offers clear images of the proximal renal artery but may miss distal lesions. An advantage is the opportunity to image the renal arteries with an agent that is not nephrotoxic. Contrast arteriography remains the “gold standard” for evaluation and identification of renal artery lesions. Potential risks include nephrotoxicity, particularly in patients with diabetes mellitus or preexisting renal insufficiency.

Some degree of renal artery obstruction may be observed in almost 50% of patients with atherosclerotic disease, and there are several approaches for evaluating the functional significance of such a lesion to predict the effect of vascular repair on blood pressure control and renal function. Each approach has varying degrees of sensitivity and specificity, and no single test is sufficiently reliable to determine a causal relationship between a renal artery lesion and hypertension. Functionally significant lesions generally occlude more than 70% of the lumen of the affected renal artery. On angiography, the presence of collateral vessels to the ischemic kidney suggests a functionally significant lesion. A lateralizing renal vein renin ratio (ratio >1.5 of affected side/contralateral side) has a 90% predictive value for a lesion that would respond to vascular repair; however, the false-negative rate for blood pressure control is

50–60%. Measurement of the pressure gradient across a renal artery lesion does not reliably predict the response to vascular repair.

In the final analysis, a decision concerning vascular repair vs. medical therapy and the type of repair procedure should be individualized. Patients with fibromuscular disease have more favorable outcomes than do patients with atherosclerotic lesions, presumably owing to their younger age, shorter duration of hypertension, and less systemic disease. Because of its low risk-versus-benefit ratio and high success rate (improvement or cure of hypertension in 90% of patients and restenosis rate of 10%), PTRA is the initial treatment of choice for these patients. Surgical revascularization may be undertaken if PTRA is unsuccessful or if a branch lesion is present. In atherosclerotic patients, vascular repair should be considered if blood pressure cannot be controlled adequately despite optimal medical therapy or if renal function deteriorates. Surgery may be the preferred initial approach for younger atherosclerotic patients without comorbid conditions; however, for most atherosclerotic patients, depending on the location of the lesion, the initial approach may be PTRA and/or stenting. Surgical revascularization may be indicated if these approaches are unsuccessful, the vascular lesion is not amenable to PTRA or stenting, or concomitant aortic surgery is required, e.g., to repair an aneurysm. A National Institutes of Health-sponsored prospective, randomized clinical trial is in progress comparing medical therapy alone with medical therapy plus renal artery stenting regarding Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL).

PRIMARY ALDOSTERONISM

Excess aldosterone production due to primary aldosteronism is a potentially curable form of hypertension. In patients with primary aldosteronism, increased aldosterone production is independent of the renin-angiotensin system, and the consequences are sodium retention, hypertension, hypokalemia, and low PRA. The reported prevalence of this disorder varies from <2% to ~15% of hypertensive individuals. In part, this variation is related to the intensity of screening and the criteria for establishing the diagnosis.

History and physical examination provide little information about the diagnosis. The age at the time of diagnosis is generally the third through fifth decade. Hypertension is usually mild to moderate but occasionally may be severe; primary aldosteronism should be considered in all patients with refractory hypertension. Hypertension in these patients may be associated with glucose intolerance. Most patients are asymptomatic; however, infrequently, polyuria, polydipsia, paresthesias, or muscle weakness may be present as

a consequence of hypokalemic alkalosis. Although aldosterone is a salt-retaining hormone, patients with primary aldosteronism rarely have edema. Renal dysfunction and cardiovascular disease are strikingly increased in patients with primary aldosteronism compared to those with primary hypertension.

In a hypertensive patient with unprovoked hypokalemia (i.e., unrelated to diuretics, vomiting, or diarrhea), the prevalence of primary aldosteronism approaches 40–50%. In patients on diuretics, serum potassium <3.1 mmol/L (<3.1 meq/L) also raises the possibility of primary aldosteronism; however, serum potassium is an insensitive and nonspecific screening test. Serum potassium is normal in $\sim 25\%$ of patients subsequently found to have an aldosterone-producing adenoma, and higher percentages of patients with other etiologies of primary aldosteronism are not hypokalemic. Additionally, hypokalemic hypertension may be a consequence of secondary aldosteronism, other mineralocorticoid- and glucocorticoid-induced hypertensive disorders, and pheochromocytoma.

The ratio of plasma aldosterone to plasma renin activity (PA/PRA) is a useful screening test. These measurements preferably are obtained in ambulatory patients in the morning. A ratio $>30:1$ in conjunction with a plasma aldosterone concentration >555 pmol/L (>20 ng/dL) reportedly has a sensitivity of 90% and a specificity of 91% for an aldosterone-producing adenoma. In a Mayo Clinic series, an aldosterone-producing adenoma subsequently was confirmed surgically in $>90\%$ of hypertensive patients with a PA/PRA ratio ≥ 20 and a plasma aldosterone concentration ≥ 415 pmol/L (≥ 15 ng/dL). There are, however, several caveats to interpreting the ratio. The cutoff for a “high” ratio is laboratory- and assay-dependent. Some antihypertensive agents may affect the ratio (e.g., aldosterone antagonists, angiotensin receptor antagonists, and ACE inhibitors may increase renin; aldosterone antagonists may increase aldosterone). Current recommendations are to withdraw aldosterone antagonists for at least 4–6 weeks before obtaining these measurements. Because aldosterone biosynthesis is potassium-dependent, hypokalemia should be corrected with oral potassium supplements prior to screening. With these caveats, the ratio has been reported to be useful as a screening test in measurements obtained with patients taking their usual antihypertensive medications. A high ratio in the absence of an elevated plasma aldosterone level is considerably less specific for primary aldosteronism since many patients with primary hypertension have low renin levels in this setting, particularly African Americans and elderly patients. In patients with renal insufficiency, the ratio may also be elevated because of decreased aldosterone clearance. In patients with an elevated PA/PRA ratio, the diagnosis of primary aldosteronism can be confirmed by demonstrating failure to suppress plasma aldosterone

to <277 pmol/L (<10 ng/dL) after IV infusion of 2 L of isotonic saline over 4 h; post-saline infusion plasma aldosterone values between 138 and 277 pmol/L (5–10 ng/dL) are not determinant. Alternative confirmatory tests include failure to suppress aldosterone (based on test specific criteria) in response to an oral NaCl load, fludrocortisone, or captopril.

Several sporadic and familial adrenal abnormalities may culminate in the syndrome of primary aldosteronism, and appropriate therapy depends on the specific etiology. The two most common causes of sporadic primary aldosteronism are an aldosterone-producing adenoma and bilateral adrenal hyperplasia. Together, they account for $>90\%$ of all patients with primary aldosteronism. The tumor is almost always unilateral, and most often measures <3 cm in diameter. Most of the remainder of these patients have bilateral adrenocortical hyperplasia (idiopathic hyperaldosteronism). Rarely, primary aldosteronism may be caused by an adrenal carcinoma or an ectopic malignancy, e.g., ovarian arrhenoblastoma. Most aldosterone-producing carcinomas, in contrast to adrenal adenomas and hyperplasia, produce excessive amounts of other adrenal steroids in addition to aldosterone. Functional differences in hormone secretion may assist in the diagnosis of adenoma vs. hyperplasia. Aldosterone biosynthesis is more responsive to ACTH in patients with adenoma and more responsive to angiotensin in patients with hyperplasia. Consequently, patients with adenoma tend to have higher plasma aldosterone in the early morning that decreases during the day, reflecting the diurnal rhythm of ACTH, whereas plasma aldosterone tends to increase with upright posture in patients with hyperplasia, reflecting the normal postural response of the renin-angiotensin-aldosterone axis. However, there is overlap in the ability of these measurements to discriminate between adenoma and hyperplasia. Rare familial forms of primary aldosteronism include glucocorticoid-remediable primary aldosteronism and familial aldosteronism types II and III. Genetic testing may assist in the diagnosis of these familial disorders.

Adrenal computed tomography (CT) should be carried out in all patients diagnosed with primary aldosteronism. High-resolution CT may identify tumors as small as 0.3 cm and is positive for an adrenal tumor 90% of the time. If the CT is not diagnostic, an adenoma may be detected by adrenal scintigraphy with 6 β -[^{131} I]iodomethyl-19-norcholesterol after dexamethasone suppression (0.5 mg every 6 h for 7 days); however, this technique has decreased sensitivity for adenomas <1.5 cm.

When carried out by an experienced radiologist, bilateral adrenal venous sampling for measurement of plasma aldosterone is the most accurate means of differentiating unilateral from bilateral forms of primary aldosteronism. The sensitivity and specificity of adrenal venous sampling (95% and 100%, respectively)

for detecting unilateral aldosterone hypersecretion are superior to those of adrenal CT; success rates are 90–96%, and complication rates are <2.5%. One frequently used protocol involves sampling for aldosterone and cortisol levels in response to ACTH stimulation. An ipsilateral/contralateral aldosterone ratio >4, with symmetric ACTH-stimulated cortisol levels, is indicative of unilateral aldosterone production.

Hypertension generally is responsive to surgery in patients with adenoma but not in patients with bilateral adrenal hyperplasia. Unilateral adrenalectomy, often done via a laparoscopic approach, is curative in 40–70% of patients with an adenoma. Transient hypoaldosteronism may occur up to 3 months postoperatively, resulting in hyperkalemia. Potassium should be monitored during this time, and hyperkalemia should be treated with potassium-wasting diuretics and with fludrocortisone, if needed. Patients with bilateral hyperplasia should be treated medically. The drug regimen for these patients, as well as for patients with an adenoma who are poor surgical candidates, should include an aldosterone antagonist and, if necessary, other potassium-sparing diuretics.

Glucocorticoid-remediable hyperaldosteronism is a rare, monogenic autosomal dominant disorder characterized by moderate to severe hypertension, often occurring at an early age. These patients may have a family history of hemorrhagic stroke at a young age. Hypokalemia is usually mild or absent. Normally, angiotensin II stimulates aldosterone production by the adrenal zona glomerulosa, whereas ACTH stimulates cortisol production in the zona fasciculata. Owing to a chimeric gene on chromosome 8, ACTH also regulates aldosterone secretion by the zona fasciculata in patients with glucocorticoid-remediable hyperaldosteronism. The consequence is overproduction in the zona fasciculata of both aldosterone and hybrid steroids (18-hydroxycortisol and 18-oxocortisol) due to oxidation of cortisol. The diagnosis may be established by urine excretion rates of these hybrid steroids that are 20 to 30 times normal or by direct genetic testing. Therapeutically, suppression of ACTH with low-dose glucocorticoids corrects the hyperaldosteronism, hypertension, and hypokalemia. Aldosterone antagonists are also therapeutic options. Patients with familial aldosteronism types II and III are treated with aldosterone antagonists or adrenalectomy.

CUSHING'S SYNDROME

Cushing's syndrome is related to excess cortisol production due either to excess ACTH secretion (from a pituitary tumor or an ectopic tumor) or to ACTH-independent adrenal production of cortisol. Hypertension occurs in 75–80% of patients with Cushing's syndrome. The mechanism of hypertension may be related to

stimulation of mineralocorticoid receptors by cortisol and increased secretion of other adrenal steroids. If clinically suspected based on phenotypic characteristics, in patients not taking exogenous glucocorticoids, laboratory screening may be carried out with measurement of 24-h excretion rates of urine free cortisol or an overnight dexamethasone-suppression test. Late night salivary cortisol is also a sensitive and convenient screening test. Further evaluation is required to confirm the diagnosis and identify the specific etiology of Cushing's syndrome. Appropriate therapy depends on the etiology.

PHEOCHROMOCYTOMA

Catecholamine-secreting tumors are located in the adrenal medulla (pheochromocytoma) or in extra-adrenal paraganglion tissue (paraganglioma) and account for hypertension in ~0.05% of patients. If unrecognized, pheochromocytoma may result in lethal cardiovascular consequences. Clinical manifestations, including hypertension, are primarily related to increased circulating catecholamines, although some of these tumors may secrete a number of other vasoactive substances. In a small percentage of patients, epinephrine is the predominant catecholamine secreted by the tumor, and these patients may present with hypotension rather than hypertension. The initial suspicion of the diagnosis is based on symptoms and/or the association of pheochromocytoma with other disorders (Table 43-4). Approximately 20% of pheochromocytomas are familial with autosomal dominant inheritance. Inherited pheochromocytomas may be associated with multiple endocrine neoplasia (MEN) type 2A and type 2B, von Hippel-Lindau disease, and neurofibromatosis (Table 43-4). Each of these syndromes is related to specific, identifiable germ-line mutations. Additionally, mutations of succinate dehydrogenase genes are associated with paraganglioma syndromes, generally characterized by head and neck paragangliomas. Laboratory testing consists of measuring catecholamines in either urine or plasma, e.g., 24-h urine metanephrine excretion or fractionated plasma free metanephrines. The urine measurement is less sensitive but more specific. Genetic screening is available for evaluating patients and relatives suspected of harboring a pheochromocytoma associated with a familial syndrome. Surgical excision is the definitive treatment of pheochromocytoma and results in cure in ~90% of patients.

MISCELLANEOUS CAUSES OF HYPERTENSION

Independent of obesity, hypertension occurs in >50% of individuals with obstructive sleep apnea. The severity of hypertension correlates with the severity of sleep

apnea. Approximately 70% of patients with obstructive sleep apnea are obese. Hypertension related to obstructive sleep apnea also should be considered in patients with drug-resistant hypertension and patients with a history of snoring. The diagnosis can be confirmed by polysomnography. In obese patients, weight loss may alleviate or cure sleep apnea and related hypertension. Continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) administered during sleep is an effective therapy for obstructive sleep apnea. With CPAP or BiPAP, patients with apparently drug-resistant hypertension may be more responsive to antihypertensive agents.

Coarctation of the aorta is the most common congenital cardiovascular cause of hypertension (**Chap. 22**). The incidence is 1–8 per 1000 live births. It is usually sporadic but occurs in 35% of children with Turner's syndrome. Even when the anatomic lesion is surgically corrected in infancy, up to 30% of patients develop subsequent hypertension and are at risk of accelerated coronary artery disease and cerebrovascular events. Patients with less severe lesions may not be diagnosed until young adulthood. Physical findings include diminished and delayed femoral pulses and a systolic pressure gradient between the right arm and the legs and, depending on the location of the coarctation, between the right and left arms. A blowing systolic murmur may be heard in the posterior left interscapular areas. The diagnosis may be confirmed by chest x-ray and transesophageal echocardiography. Therapeutic

options include surgical repair and balloon angioplasty, with or without placement of an intravascular stent. Subsequently, many patients do not have a normal life expectancy but may have persistent hypertension, with death due to ischemic heart disease, cerebral hemorrhage, or aortic aneurysm.

Several additional endocrine disorders, including thyroid diseases and acromegaly, cause hypertension. Mild diastolic hypertension may be a consequence of hypothyroidism, whereas hyperthyroidism may result in systolic hypertension. Hypercalcemia of any etiology, the most common being primary hyperparathyroidism, may result in hypertension. Hypertension also may be related to a number of prescribed or over-the-counter medications.

MONOGENIC HYPERTENSION

In addition to glucocorticoid-remediable primary aldosteronism, a number of rare forms of monogenic hypertension have been identified (Table 43–4). These disorders may be recognized by their characteristic phenotypes, and in many instances the diagnosis may be confirmed by genetic analysis. Several inherited defects in adrenal steroid biosynthesis and metabolism result in mineralocorticoid-induced hypertension and hypokalemia. In patients with a 17α -hydroxylase deficiency, synthesis of sex hormones and cortisol is decreased (**Fig. 43-3**). Consequently, these individuals do not

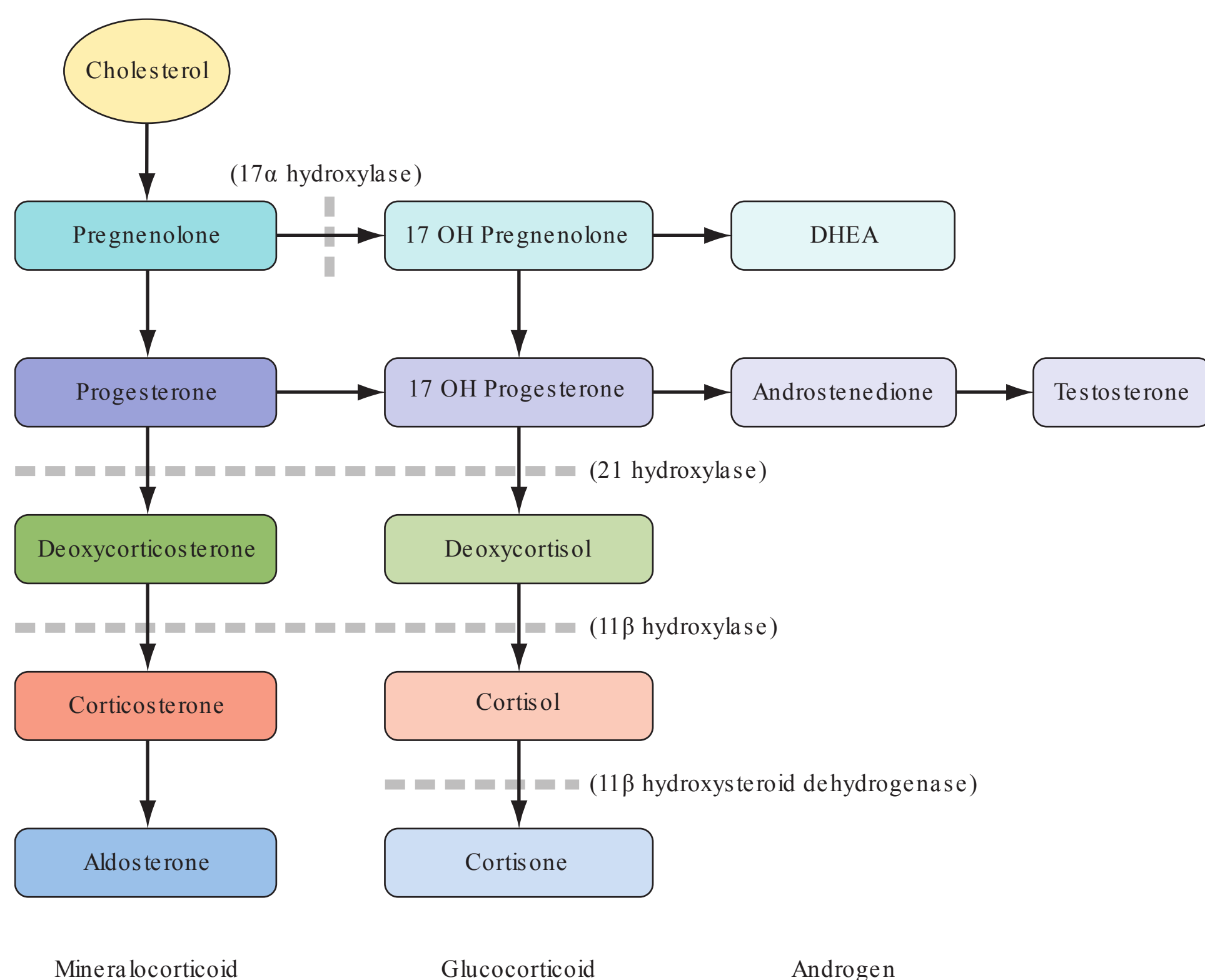


FIGURE 43-3

Adrenal enzymatic defects. DHEA, dehydroepiandrosterone.

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mature sexually; males may present with pseudohermaphroditism and females with primary amenorrhea and absent secondary sexual characteristics. Because cortisol-induced negative feedback on pituitary ACTH production is diminished, ACTH-stimulated adrenal steroid synthesis proximal to the enzymatic block is increased. Hypertension and hypokalemia are consequences of increased synthesis of mineralocorticoids proximal to the enzymatic block, particularly desoxycorticosterone. Increased steroid production and, hence, hypertension may be treated with low-dose glucocorticoids. An 11 β -hydroxylase deficiency results in a salt-retaining adrenogenital syndrome that occurs in 1 in 100,000 live births. This enzymatic defect results in decreased cortisol synthesis, increased synthesis of mineralocorticoids (e.g., desoxycorticosterone), and shunting of steroid biosynthesis into the androgen pathway. In the severe form, the syndrome may present early in life, including the newborn period, with virilization and ambiguous genitalia in females and penile enlargement in males, or in older children as precocious puberty and short stature. Acne, hirsutism, and menstrual irregularities may be the presenting features when the disorder is first recognized in adolescence or early adulthood. Hypertension is less common in the late-onset forms. Patients with an 11 β -hydroxysteroid dehydrogenase deficiency have an impaired capacity to metabolize cortisol to its inactive metabolite, cortisone, and hypertension is related to activation of mineralocorticoid receptors by cortisol. This defect may be inherited or acquired, due to licorice-containing glycyrrhizin acid. The same substance is present in the paste of several brands of chewing tobacco. The defect in Liddle's syndrome results from constitutive activation of amiloride-sensitive epithelial sodium channels on the distal renal tubule, resulting in excess sodium reabsorption; the syndrome is ameliorated by amiloride. Hypertension exacerbated in pregnancy may be due to activation of the mineralocorticoid receptor by progesterone.

APPROACH TO THE PATIENT

Hypertension

HISTORY The initial assessment of a hypertensive patient should include a complete history and physical examination to confirm a diagnosis of hypertension, screen for other cardiovascular disease risk factors, screen for secondary causes of hypertension, identify cardiovascular consequences of hypertension and other comorbidities, assess blood pressure–related lifestyles, and determine the potential for intervention.

Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. Although

popularly considered a symptom of elevated arterial pressure, headache generally occurs only in patients with severe hypertension. Characteristically, a “hypertensive headache” occurs in the morning and is localized to the occipital region. Other nonspecific symptoms that may be related to elevated blood pressure include dizziness, palpitations, easy fatigability, and impotence. When symptoms are present, they are generally related to hypertensive cardiovascular disease or to manifestations of secondary hypertension. **Table 43-5** lists salient features that should be addressed in obtaining a history from a hypertensive patient.

MEASUREMENT OF BLOOD PRESSURE Reliable measurements of blood pressure depend on attention to the details of the technique and conditions of the measurement. Proper training of observers, positioning of the patient, and selection of cuff size are essential. Owing to recent regulations preventing the use of mercury because of concerns about its potential toxicity, most of these measurements are made with aneroid sphygmomanometers or with oscillometric devices. These instruments should be calibrated periodically, and their accuracy confirmed. Before the blood pressure measurement is taken, the individual should be seated quietly in a chair (not the exam table) with feet on the floor for 5 min in a private, quiet setting with a comfortable room temperature. At least two measurements should be made. The center of the cuff should be at heart level, and the width of the bladder cuff should equal at least 40% of the arm circumference; the length of the cuff bladder should encircle at least 80% of the arm circumference. It is important to pay attention to cuff placement, stethoscope placement, and

TABLE 43-5

PATIENT’S RELEVANT HISTORY
Duration of hypertension
Previous therapies: responses and side effects
Family history of hypertension and cardiovascular disease
Dietary and psychosocial history
Other risk factors: weight change, dyslipidemia, smoking, diabetes, physical inactivity
Evidence of secondary hypertension: history of renal disease; change in appearance; muscle weakness; spells of sweating, palpitations, tremor; erratic sleep, snoring, daytime somnolence; symptoms of hypo- or hyperthyroidism; use of agents that may increase blood pressure
Evidence of target organ damage: history of TIA, stroke, transient blindness; angina, myocardial infarction, congestive heart failure; sexual function
Other comorbidities

Abbreviation: TIA, transient ischemic attack.

the rate of deflation of the cuff (2 mmHg/s). Systolic blood pressure is the first of at least two regular “tapping” Korotkoff sounds, and diastolic blood pressure is the point at which the last regular Korotkoff sound is heard. In current practice, a diagnosis of hypertension generally is based on seated, of ce measurements.

Currently available ambulatory monitors are fully automated, use the oscillometric technique, and typically are programmed to take readings every 15–30 min. Twenty-four-hour ambulatory blood pressure monitoring more reliably predicts cardiovascular disease risk than do of ce measurements. However, ambulatory monitoring is not used routinely in clinical practice and generally is reserved for patients in whom white coat hypertension is suspected. T e Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has also recommended ambulatory monitoring for treatment resistance, symptomatic hypotension, autonomic failure, and episodic hypertension.

PHYSICALEXAMINATION Body habitus, including weight and height, should be noted. At the initial examination, blood pressure should be measured in both arms and preferably in the supine, sitting, and standing positions to evaluate for postural hypotension. Even if the femoral pulse is normal to palpation, arterial pressure should be measured at least once in the lower extremity in patients in whom hypertension is discovered before age 30. Heart rate also should be recorded. Hypertensive individuals have an increased prevalence of atrial fibrillation. T e neck should be palpated for an enlarged thyroid gland, and patients should be assessed for signs of hypo- and hyperthyroidism. Examination of blood vessels may provide clues about underlying vascular disease and should include fundoscopic examination, auscultation for bruits over the carotid and femoral arteries, and palpation of femoral and pedal pulses. T e retina is the only tissue in which arteries and arterioles can be examined directly. With increasing severity of hypertension and atherosclerotic disease, progressive fundoscopic changes include increased arteriolar light reflex, arteriovenous crossing defects, hemorrhages and exudates, and, in patients with malignant hypertension, papilledema. Examination of the heart may reveal a loud second heart sound due to closure of the aortic valve and an S₄ gallop attributed to atrial contraction against a noncompliant left ventricle. Left ventricular hypertrophy may be detected by an enlarged, sustained, and laterally displaced apical impulse. An abdominal bruit, particularly a bruit that lateralizes and extends throughout systole into diastole, raises the possibility of renovascular hypertension. Kidneys of patients with polycystic kidney disease may be palpable in the abdomen. T e physical examination also should include evaluation for signs of CHF and a neurologic examination.

TABLE 43-6

BASIC LABORATORY TESTS FOR INITIAL EVALUATION	
SYSTEM	TEST
Renal	Microscopic urinalysis, albumin excretion, serum BUN and/or creatinine
Endocrine	Serum sodium, potassium, calcium, ?TSH
Metabolic	Fasting blood glucose, total cholesterol, HDL and LDL (often computed) cholesterol, triglycerides
Other	Hematocrit, electrocardiogram

Abbreviations: BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

LABORATORY TESTING Table 43-6 lists recommended laboratory tests in the initial evaluation of hypertensive patients. Repeat measurements of renal function, serum electrolytes, fasting glucose, and lipids may be obtained after the introduction of a new antihypertensive agent and then annually or more frequently if clinically indicated. More extensive laboratory testing is appropriate for patients with apparent drug-resistant hypertension or when the clinical evaluation suggests a secondary form of hypertension.

TREATMENT Hypertension

LIFESTYLEINTERVENTIONS Implementation of lifestyles that favorably affect blood pressure has implications for both the prevention and the treatment of hypertension. Health-promoting lifestyle modifications are recommended for individuals with prehypertension and as an adjunct to drug therapy in hypertensive individuals. T ese interventions should address overall cardiovascular disease risk. Although the impact of lifestyle interventions on blood pressure is more pronounced in persons with hypertension, in short-term trials, weight loss and reduction of dietary NaCl have been shown to prevent the development of hypertension. In hypertensive individuals, even if these interventions do not produce a suf cient reduction in blood pressure to avoid drug therapy, the number of medications or doses required for blood pressure control may be reduced. Dietary modifications that effectively lower blood pressure are weight loss, reduced NaCl intake, increased potassium intake, moderation of alcohol consumption, and an overall healthy dietary pattern (Table 43-7).

Prevention and treatment of obesity are important for reducing blood pressure and cardiovascular disease risk. In short-term trials, even modest weight loss can lead to a

TABLE 43-7

LIFESTYLE MODIFICATIONS TO MANAGE HYPERTENSION	
Weight reduction	Attain and maintain BMI <25 kg/m ²
Dietary salt reduction	<6 g NaCl/d
Adapt DASH-type dietary plan	Diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat
Moderation of alcohol consumption	For those who drink alcohol, consume ≤2 drinks/day in men and ≤1 drink/day in women
Physical activity	Regular aerobic activity, e.g., brisk walking for 30 min/d

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension (trial).

reduction of blood pressure and an increase in insulin sensitivity. Average blood pressure reductions of 6.3/3.1 mmHg have been observed with a reduction in mean body weight of 9.2 kg. Regular physical activity facilitates weight loss, decreases blood pressure, and reduces the overall risk of cardiovascular disease. Blood pressure may be lowered by 30 min of moderately intense physical activity, such as brisk walking, 6–7 days a week, or by more intense, less frequent workouts.

There is individual variability in the sensitivity of blood pressure to NaCl, and this variability may have a genetic basis. Based on results of meta-analyses, lowering of blood pressure by limiting daily NaCl intake to 4.4–7.4 g (75–125 meq) results in blood pressure reductions of 3.7–4.9/0.9–2.9 mmHg in hypertensive individuals and lesser reductions in normotensive individuals. Several long-term, prospective, randomized clinical trials have reported that a reduced salt intake results in a decreased incidence of cardiovascular events. Although reduced salt intakes are generally recommended for both the prevention and treatment of hypertension, overly rigorous salt restriction may have adverse cardiovascular outcomes in diabetic patients and in patients with CHF aggressively treated with diuretics. Potassium and calcium supplementation have inconsistent, modest antihypertensive effects, and, independent of blood pressure, potassium supplementation may be associated with reduced stroke mortality. Consuming three or more alcoholic drinks per day (a standard drink contains ~14 g ethanol) is associated with higher blood pressures, and a reduction of alcohol consumption is associated with a reduction of blood pressure. In patients with advanced renal disease, dietary protein restriction may have a modest effect in mitigating renal damage by reducing the intrarenal transmission of systemic arterial pressure.

The DASH (Dietary Approaches to Stop Hypertension) trial convincingly demonstrated that over an 8-week period

a diet high in fruits, vegetables, and low-fat dairy products lowers blood pressure in individuals with high-normal blood pressures or mild hypertension. Reduction of daily NaCl intake to <6 g (100 meq) augmented the effect of this diet on blood pressure. Fruits and vegetables are enriched sources of potassium, magnesium, and fiber, and dairy products are an important source of calcium.

PHARMACOLOGICTHERAPY Drug therapy is recommended for individuals with blood pressures ≥140/90 mmHg. The degree of benefit derived from antihypertensive agents is related to the magnitude of the blood pressure reduction. Lowering systolic blood pressure by 10–12 mmHg and diastolic blood pressure by 5–6 mmHg confers relative risk reductions of 35–40% for stroke and 12–16% for CHD within 5 years of the initiation of treatment. Risk of heart failure is reduced by >50%. Hypertension control is the single most effective intervention for slowing the rate of progression of hypertension-related kidney disease.

There is considerable variation in individual responses to different classes of antihypertensive agents, and the magnitude of response to any single agent may be limited by activation of counter-regulatory mechanisms. Most available agents reduce systolic blood pressure by 7–13 mmHg and diastolic blood pressure by 4–8 mmHg when corrected for placebo effect. More often than not, combinations of agents, with complementary antihypertensive mechanisms, are required to achieve goal blood pressure reductions. Selection of antihypertensive agents and combinations of agents should be individualized, taking into account age, severity of hypertension, other cardiovascular disease risk factors, comorbid conditions, and practical considerations related to cost, side effects, and frequency of dosing (Table 43-8).

Diuretics Low-dose thiazide diuretics may be used alone or in combination with other antihypertensive drugs. Thiazides inhibit the Na⁺/Cl[−] pump in the distal convoluted tubule and hence increase sodium excretion. In the long term, they also may act as vasodilators. Thiazides are safe, efficacious, inexpensive, and reduce clinical events. They provide additive blood pressure-lowering effects when combined with beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs). In contrast, addition of a diuretic to a calcium channel blocker is less effective. Usual doses of hydrochlorothiazide range from 6.25–50 mg/d. Owing to an increased incidence of metabolic side effects (hypokalemia, insulin resistance, increased cholesterol), higher doses generally are not recommended. Chlorthalidone is a diuretic structurally similar to hydrochlorothiazide, and like hydrochlorothiazide, it blocks sodium-chloride cotransport in the early distal tubule. However, chlorthalidone has a longer half-life (40–60 h vs. 9–15 h) and an antihypertensive potency ~1.5–2.0 times that of hydrochlorothiazide. Potassium loss is also greater with chlorthalidone. Two potassium-sparing diuretics, amiloride and triamterene, act by inhibiting epithelial sodium channels in the distal nephron. These agents are weak

TABLE 43-8

EXAMPLES OF ORAL DRUGS USED IN TREATMENT OF HYPERTENSION					
DRUG CLASS	EXAMPLES	USUAL TOTAL DAILY DOSE ^a (DOSING FREQUENCY/ DAY)	OTHER INDICATIONS	CONTRAINDICATIONS/ CAUTIONS	
Diuretics					
Thiazides	Hydrochlorothiazide	6.25–50 mg (1–2)	CHF due to systolic dysfunction, renal failure	Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia	
	Chlorthalidone	25–50 mg (1)			
Loop diuretics	Furosemide	40–80 mg (2–3)		CHF due to systolic dysfunction, primary aldosteronism	Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
	Ethacrynic acid	50–100 mg (2–3)			
Aldosterone antagonists	Spironolactone	25–100 mg (1–2)	CHF due to systolic dysfunction, primary aldosteronism	Renal failure, hyperkalemia	
	Eplerenone	50–100 mg (1–2)			
K ⁺ retaining	Amiloride	5–10 mg (1–2)			Renal failure, hyperkalemia
	Triamterene	50–100 mg (1–2)			
Beta blockers					
Cardioselective	Atenolol	25–100 mg (1)	Angina, CHF due to systolic dysfunction, post-MI, sinus tachycardia, ventricular tachyarrhythmias	Asthma, COPD, 2nd- or 3rd-degree heart block, sick-sinus syndrome	
Nonselective	Metoprolol	25–100 mg (1–2)			
	Propranolol	40–160 mg (2)			
	Propranolol LA	60–180 (1)			
Combined alpha/beta	Labetalol	200–800 mg (2)	?Post-MI, CHF		
	Carvedilol	12.5–50 mg (2)			
Alpha antagonists					
Selective	Prazosin	2–20 mg (2–3)	Prostatism		
	Doxazosin	1–16 mg (1)			
	Terazosin	1–10 mg (1–2)			
Nonselective	Phenoxybenzamine	20–120 mg (2–3)	Pheochromocytoma		
Sympatholytics					
Central	Clonidine	0.1–0.6 mg (2)			
	Clonidine patch	0.1–0.3 mg (1/week)			
	Methyldopa	250–1000 mg (2)			
	Reserpine	0.05–0.25 mg (1)			
	Guanfacine	0.5–2 mg (1)			
ACE inhibitors	Captopril	25–200 mg (2)	Post-MI, coronary syndromes, CHF with low ejection fraction, nephropathy	Acute renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia	
	Lisinopril	10–40 mg (1)			
	Ramipril	2.5–20 mg (1–2)			
Angiotensin II antagonists	Losartan	25–100 mg (1–2)	CHF with low ejection fraction, nephropathy, ACE inhibitor cough	Renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia	
	Valsartan	80–320 mg (1)			
	Candesartan	2–32 mg (1–2)			
Renin inhibitors	Aliskiren	150–300 mg (1)	Diabetic nephropathy	Pregnancy	
Calcium antagonists					
Dihydropyridines	Nifedipine (long-acting)	30–60 mg (1)	Post-MI, supraventricular tachycardias, angina	2nd- or 3rd-degree heart block	
Nondihydropyridines	Verapamil (long-acting)	120–360 mg (1–2)			
	Diltiazem (long-acting)	180–420 mg (1)			
Direct vasodilators	Hydralazine	25–100 mg (2)		Severe coronary artery disease	
	Minoxidil	2.5–80 mg (1–2)			

^aAt the initiation of therapy, lower doses may be preferable for elderly patients and for select combinations of antihypertensive agents. Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

antihypertensive agents but may be used in combination with a thiazide to protect against hypokalemia. The main pharmacologic target for loop diuretics is the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter in the thick ascending limb of the loop of Henle. Loop diuretics generally are reserved for hypertensive patients with reduced glomerular filtration rates (reflected in serum creatinine $>220\text{ }\mu\text{mol/L}$ [$>2.5\text{ mg/dL}$]), CHF, or sodium retention and edema for some other reason, such as treatment with a potent vasodilator, e.g., minoxidil.

Blockers of the Renin–Angiotensin System ACEIs decrease the production of angiotensin II, increase bradykinin levels, and reduce sympathetic nervous system activity. ARBs provide selective blockade of AT_1 receptors, and the effect of angiotensin II on unblocked AT_2 receptors may augment their hypotensive effect. Both classes of agents are effective antihypertensive agents that may be used as monotherapy or in combination with diuretics, calcium antagonists, and alpha blocking agents. ACEIs and ARBs improve insulin action and ameliorate the adverse effects of diuretics on glucose metabolism. Although the overall impact on the incidence of diabetes is modest, compared with amlodipine (a calcium antagonist), valsartan (an ARB) has been shown to reduce the risk of developing diabetes in high-risk hypertensive patients. ACEI/ARB combinations are less effective in lowering blood pressure than is the case when either class of these agents is used in combination with other classes of agents. In patients with vascular disease or a high risk of diabetes, combination ACEI/ARB therapy has been associated with more adverse events (e.g., cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure) without increases in benefit.

Side effects of ACEIs and ARBs include functional renal insufficiency due to efferent renal arteriolar dilation in a kidney with a stenotic lesion of the renal artery. Additional predisposing conditions to renal insufficiency induced by these agents include dehydration, CHF, and use of nonsteroidal anti-inflammatory drugs. Dry cough occurs in $\sim 15\%$ of patients, and angioedema occurs in $<1\%$ of patients taking ACEIs. Angioedema occurs most commonly in individuals of Asian origin and more commonly in African Americans than in whites. Hyperkalemia due to hypoaldosteronism is an occasional side effect of both ACEIs and ARBs.

An alternative approach to blocking the renin-angiotensin system has recently been introduced into clinical practice for the treatment of hypertension: direct renin inhibitors. Blockade of the renin-angiotensin system is more complete with renin inhibitors than with ACEIs or ARBs. Aliskiren is the first of a class of oral, nonpeptide competitive inhibitors of the enzymatic activity of renin. Monotherapy with aliskiren seems to be as effective as an ACEI or ARB for lowering blood pressure, but not more effective. Further blood reductions may be achieved when aliskiren is used in combination with a thiazide diuretic or a calcium antagonist. Currently, aliskiren is not considered a first-line antihypertensive agent.

Aldosterone Antagonists Spironolactone is a nonselective aldosterone antagonist that may be used alone or in combination with a thiazide diuretic. It may be a particularly effective agent in patients with low-renin primary hypertension, resistant hypertension, and primary aldosteronism. In patients with CHF, low-dose spironolactone reduces mortality and hospitalizations for heart failure when given in addition to conventional therapy with ACEIs, digoxin, and loop diuretics. Because spironolactone binds to progesterone and androgen receptors, side effects may include gynecomastia, impotence, and menstrual abnormalities. These side effects are circumvented by a newer agent, eplerenone, which is a selective aldosterone antagonist.

Beta Blockers β -Adrenergic receptor blockers lower blood pressure by decreasing cardiac output, due to a reduction of heart rate and contractility. Other proposed mechanisms by which beta blockers lower blood pressure include a central nervous system effect and inhibition of renin release. Beta blockers are particularly effective in hypertensive patients with tachycardia, and their hypotensive potency is enhanced by coadministration with a diuretic. In lower doses, some beta blockers selectively inhibit cardiac β_1 receptors and have less influence on β_2 receptors on bronchial and vascular smooth muscle cells; however, there seems to be no difference in the antihypertensive potencies of cardioselective and nonselective beta blockers. Some beta blockers have intrinsic sympathomimetic activity, although it is uncertain whether this constitutes an overall advantage or disadvantage in cardiac therapy. Beta blockers without intrinsic sympathomimetic activity decrease the rate of sudden death, overall mortality, and recurrent myocardial infarction. In patients with CHF, beta blockers have been shown to reduce the risks of hospitalization and mortality. Overall, beta blockers may be less protective against cardiovascular and cerebrovascular endpoints, and some beta blockers may have less effect on central aortic pressure than other classes of antihypertensive agents. However, beta blockers remain appropriate therapy for hypertensive patients with concomitant heart disease and related comorbidities. Carvedilol and labetalol block both β receptors and peripheral α -adrenergic receptors. The potential advantages of combined β - and α -adrenergic blockade in treating hypertension remain to be determined. Nebivolol represents another class of cardioselective beta blockers that has additional vasodilator actions related to enhancement of nitric oxide activity. Whether this confers greater clinical effectiveness remains to be determined.

α -Adrenergic Blockers Postsynaptic, selective α -adrenoreceptor antagonists lower blood pressure by decreasing peripheral vascular resistance. They are effective antihypertensive agents used either as monotherapy or in combination with other agents. However, in clinical trials of hypertensive patients, alpha blockade has not been shown to reduce cardiovascular morbidity and mortality or to provide as much protection against CHF as other classes of antihypertensive agents. These agents are also effective in treating lower urinary tract

symptoms in men with prostatic hypertrophy. Nonselective α -adrenoreceptor antagonists bind to postsynaptic and presynaptic receptors and are used primarily for the management of patients with pheochromocytoma.

Sympatholytic Agents Centrally acting α_2 sympathetic agonists decrease peripheral resistance by inhibiting sympathetic outflow. They may be particularly useful in patients with autonomic neuropathy who have wide variations in blood pressure due to baroreceptor denervation. Drawbacks include somnolence, dry mouth, and rebound hypertension on withdrawal. Peripheral sympatholytics decrease peripheral resistance and venous constriction by depleting nerve terminal norepinephrine. Although they are potentially effective antihypertensive agents, their usefulness is limited by orthostatic hypotension, sexual dysfunction, and numerous drug-drug interactions. Rebound hypertension is another concern with abrupt cessation of drugs with a short half-life.

Calcium Channel Blockers Calcium antagonists reduce vascular resistance through L-channel blockade, which reduces intracellular calcium and blunts vasoconstriction. This is a heterogeneous group of agents that includes drugs in the following three classes: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and 1,4-dihydropyridines (nifedipine-like). Used alone and in combination with other agents (ACEIs, beta blockers, α_1 -adrenergic blockers), calcium antagonists effectively lower blood pressure; however, it is unclear if adding a diuretic to a calcium blocker results in a further lowering of blood pressure. Side effects of flushing, headache, and edema with dihydropyridine use are related to their potencies as arteriolar dilators; edema is due to an increase in transcapillary pressure gradients, not to net salt and water retention.

Direct Vasodilators Direct vasodilators decrease peripheral resistance and concomitantly activate mechanisms that defend arterial pressure, notably the sympathetic nervous system, the renin-angiotensin-aldosterone system, and sodium retention. Usually, they are not considered first-line agents but are most effective when added to a combination that includes a diuretic and a beta blocker. Hydralazine is a potent direct vasodilator that has antioxidant and nitric oxide-enhancing actions, and minoxidil is a particularly potent agent and is used most frequently in patients with renal insufficiency who are refractory to all other drugs. Hydralazine may induce a lupus-like syndrome, and side effects of minoxidil include hypertrichosis and pericardial effusion. Intravenous nitroprusside can be used to treat malignant hypertension and life-threatening left ventricular heart failure associated with elevated arterial pressure.

COMPARISONS OF ANTIHYPERTENSIVES Based on pooling results from clinical trials, meta-analyses of the efficacy of different classes of antihypertensive agents suggest essentially equivalent blood pressure-lowering effects of the following six major classes of antihypertensive agents when used as monotherapy: thiazide diuretics, beta blockers, ACEIs, ARBs, calcium

antagonists, and α_1 blockers. On average, standard doses of most antihypertensive agents reduce blood pressure by 8–10/4–7 mmHg; however, there may be subgroup differences in responsiveness. Younger patients may be more responsive to beta blockers and ACEIs, whereas patients over age 50 may be more responsive to diuretics and calcium antagonists. There is a limited relationship between plasma renin and blood pressure response. Patients with high-renin hypertension may be more responsive to ACEIs and ARBs than to other classes of agents, whereas patients with low-renin hypertension are more responsive to diuretics and calcium antagonists. Hypertensive African Americans tend to have low renin and may require higher doses of ACEIs and ARBs than whites for optimal blood pressure control, although this difference is abolished when these agents are combined with a diuretic. Beta blockers also appear to be less effective than thiazide diuretics in African Americans than in non-African Americans. Early pharmacogenetic studies, utilizing either a candidate gene approach or genome-wide scans, have shown associations of gene polymorphisms with blood pressure responsiveness to specific antihypertensive drugs. However, the reported effects have generally been too small to affect clinical decisions, and associated polymorphisms remain to be confirmed. Currently, in practical terms, the presence of comorbidities often influences the selection of antihypertensive agents.

A meta-analysis of more than 30 randomized trials of blood pressure-lowering therapy indicates that for a given reduction in blood pressure, the major drug classes seem to produce similar overall net effects on total cardiovascular events. In both nondiabetic and diabetic hypertensive patients, most trials have failed to show significant differences in cardiovascular outcomes with different drug regimens as long as equivalent decreases in blood pressure were achieved. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that the occurrence of CHD and nonfatal myocardial infarction, as well as overall mortality, was virtually identical in hypertensive patients treated with either an ACEI (lisinopril), a diuretic (chlorthalidone), or a calcium antagonist (amlodipine).

However, in specific patient groups, ACEIs may have particular advantages, beyond that of blood pressure control, in reducing cardiovascular and renal outcomes. ACEIs and ARBs decrease intraglomerular pressure and proteinuria and may retard the rate of progression of renal insufficiency, not totally accounted for by their hypotensive effects, in both diabetic and nondiabetic renal diseases. In patients with type 2 diabetes, treatment with an ACEI, an ARB, or aliskiren decreases proteinuria and delays the progression of renal disease. In experimental models of hypertension and diabetes, renal protection with aliskiren is comparable to that with ACEIs and ARBs. However, in patients with type 2 diabetes, addition of aliskiren to an ACEI provides no additional protection against cardiovascular or renal disease and may be associated with more adverse outcomes. Among African

Americans with hypertension-related renal disease, ACEIs appear to be more effective than beta blockers or dihydropyridine calcium channel blockers in slowing, although not preventing, the decline of glomerular filtration rate. The renoprotective effect of these renin-angiotensin blockers, compared with other antihypertensive drugs, is less obvious at lower blood pressures. In most patients with hypertension and heart failure due to systolic and/or diastolic dysfunction, the use of diuretics, ACEIs or ARBs, and beta blockers is recommended to improve survival. Independent of blood pressure, in both hypertensive and normotensive individuals, ACEIs attenuate the development of left ventricular hypertrophy, improve symptomatology and risk of death from CHF, and reduce morbidity and mortality rates in post-myocardial infarction patients. Similar benefits in cardiovascular morbidity and mortality rates in patients with CHF have been observed with the use of ARBs. ACEIs provide better coronary protection than do calcium channel blockers, whereas calcium channel blockers provide more stroke protection than do either ACEIs or beta blockers. Results of a large, double-blind, prospective clinical trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH Trial]) indicated that combination treatment with an ACEI (benazepril) plus a calcium antagonist (amlodipine) was superior to treatment with the ACEI plus a diuretic (hydrochlorothiazide) in reducing the risk of cardiovascular events and death among high-risk patients with hypertension. However, the combination of an ACEI and a diuretic has recently been shown to produce major reductions in morbidity and mortality in the very elderly.

After a stroke, combination therapy with an ACEI and a diuretic, but not with an ARB, has been reported to reduce the rate of recurrent stroke. Some of these apparent differences may reflect differences in trial design and/or patient groups.

There is a recent resurgence of interest in two nonpharmacologic, antihypertensive therapies that interrupt sympathetic outflow: (1) device-based carotid baroreflex activation by electrical stimulation of the carotid sinus; and (2) endovascular radiofrequency ablation of the renal sympathetic nerves. Whereas renal denervation is a minimally invasive procedure, carotid baroreceptor stimulation is a surgical procedure, usually performed under general anesthesia, that currently involves implanting electrodes on both the right and left carotid arteries. Both interventions inhibit sympathetic drive and decrease blood pressure by increasing the capacity of the kidney to excrete sodium and by decreasing renin release. Sustained activation of the baroreflex most likely lowers blood pressure by other mechanisms as well. Clinical experience with these interventions is limited. In the short term, blood pressure is lowered in 75–80% of patients, and the magnitude of the blood pressure reduction is similar for both procedures. To date, the most impressive results have been observed in patients with “resistant” hypertension

and patients with obesity-related hypertension. Awaiting the results of long-term, multicenter clinical trials to evaluate their efficacy and safety, it remains to be seen whether these interventions will be adopted into clinical practice.

BLOOD PRESSURE GOALS OF ANTIHYPERTENSIVE THERAPY Based on clinical trial data, the maximum protection against combined cardiovascular endpoints is achieved with pressures <135–140 mmHg for systolic blood pressure and <80–85 mmHg for diastolic blood pressure; however, treatment has not reduced cardiovascular disease risk to the level in nonhypertensive individuals. In diabetic patients, effective blood pressure control reduces the risk of cardiovascular events and death as well as the risk for microvascular disease (nephropathy, retinopathy). Although guidelines for hypertension control have recommended more aggressive blood pressure targets (e.g., office or clinic blood pressure <130/80 mmHg) for patients with diabetes, CHD, chronic kidney disease, or additional cardiovascular disease risk factors, recent evidence suggests that overly aggressive targets for blood pressure control may not be advantageous, particularly in high-risk patients. For example, among hypertensive patients with diabetes and coronary heart disease, “tight control” of systolic blood pressure (<130 mmHg) is not associated with improved cardiovascular outcomes. The concept of a “J-curve” suggests that the risk of cardiovascular events increases at blood pressures that are either too high or too low. Theoretically blood pressures that are too low may exceed the autoregulatory capacity of cerebral, coronary, and renal blood flows. There is some suggestive evidence from recent randomized clinical trials for a J-shaped relationship between blood pressure and cardiovascular outcomes (including all-cause mortality) in high-risk patients. Consequently, caution should be exercised in lowering blood pressure <130/80 mmHg in patients with diabetes, CHD, and other high-risk patients. In patients with chronic renal insufficiency, a small, nonprogressive increase in the serum creatinine concentration may occur. This generally reflects a hemodynamic response, not structural renal injury, indicating that intraglomerular pressure has been reduced. Blood pressure control should not be allowed to deteriorate in order to prevent the modest creatinine rise. Among older patients with isolated systolic hypertension, further lowering of diastolic blood pressure does not result in harm. However, relatively little information is available concerning the risk-versus-benefit ratio of antihypertensive therapy in individuals >80 years of age, and in this population, gradual blood pressure reduction to a less aggressive target level of control may be appropriate.

To achieve recommended blood pressure goals, the majority of individuals with hypertension will require treatment with more than one drug. Three or more drugs frequently are needed in patients with diabetes and renal insufficiency. For most agents, reduction of blood pressure at half-standard doses is only ~20% less than at standard doses. Appropriate combinations of agents at these lower doses may have additive or almost additive effects on blood pressure with a lower incidence of side effects.

The term resistant hypertension refers to patients with blood pressures persistently $>140/90$ mmHg despite taking three or more antihypertensive agents, including a diuretic. Resistant or difficult-to-control hypertension is more common in patients >60 years than in younger patients. Resistant hypertension may be related to “pseudoresistance” (high office blood pressures and lower home blood pressures), nonadherence to therapy, identifiable causes of hypertension (including obesity and excessive alcohol intake), and the use of any of a number of nonprescription and prescription drugs (Table 43-3). Rarely, in older patients, pseudohypertension may be related to the inability to measure blood pressure accurately in severely sclerotic arteries. This condition is suggested if the radial pulse remains palpable despite occlusion of the brachial artery by the cuff (Osler maneuver). The actual blood pressure can be determined by direct intra-arterial measurement. Evaluation of patients with resistant hypertension might include home blood pressure monitoring to determine if office blood pressures are representative of the usual blood pressure. A more extensive evaluation for a secondary form of hypertension should be undertaken if no other explanation for hypertension resistance becomes apparent.

HYPERTENSIVE EMERGENCIES Probably due to the widespread availability of antihypertensive therapy, in the United States there has been a decline in the numbers of patients presenting with “crisis levels” of blood pressure. Most patients who present with severe hypertension are chronically hypertensive, and in the absence of acute end organ damage, precipitous lowering of blood pressure may result in significant morbidity and should be avoided. The key to successful management of severe hypertension is to differentiate hypertensive crises from hypertensive urgencies. The degree of target organ damage, rather than the level of blood pressure alone, determines the rapidity with which blood pressure should be lowered. **Tables 43-9** and **43-10** list a number of hypertension-related emergencies and recommended therapies.

Malignant hypertension is a syndrome associated with an abrupt increase of blood pressure in a patient with underlying hypertension or related to the sudden onset of hypertension in a previously normotensive individual. The absolute level of blood pressure is not as important as its rate of rise. Pathologically, the syndrome is associated with diffuse necrotizing vasculitis, arteriolar thrombi, and fibrin deposition in arteriolar walls. Fibrinoid necrosis has been observed in arterioles of kidney, brain, retina, and other organs. Clinically, the syndrome is recognized by progressive retinopathy (arteriolar spasm, hemorrhages, exudates, and papilledema), deteriorating renal function with proteinuria, microangiopathic hemolytic anemia, and encephalopathy. Historic inquiry should include questions about the use of monoamine oxidase inhibitors and recreational drugs (e.g., cocaine, amphetamines).

Although blood pressure should be lowered rapidly in patients with hypertensive encephalopathy, there are inherent risks of overly aggressive therapy. In hypertensive individuals,

TABLE 43-9

PREFERRED PARENTERAL DRUGS FOR SELECTED HYPERTENSIVE EMERGENCIES	
Hypertensive encephalopathy	Nitroprusside, nicardipine, labetalol
Malignant hypertension (when IV therapy is indicated)	Labetalol, nicardipine, nitroprusside, enalaprilat
Stroke	Nicardipine, labetalol, nitroprusside
Myocardial infarction/unstable angina	Nitroglycerin, nicardipine, labetalol, esmolol
Acute left ventricular failure	Nitroglycerin, enalaprilat, loop diuretics
Aortic dissection	Nitroprusside, esmolol, labetalol
Adrenergic crisis	Phentolamine, nitroprusside
Postoperative hypertension	Nitroglycerin, nitroprusside, labetalol, nicardipine
Preeclampsia/eclampsia of pregnancy	Hydralazine, labetalol, nicardipine

Source: Adapted from DG Viddt, in S Oparil, MA Weber (eds): Hypertension, 2nd ed. Philadelphia, Elsevier Saunders, 2005.

the upper and lower limits of autoregulation of cerebral blood flow are shifted to higher levels of arterial pressure, and rapid lowering of blood pressure to below the lower limit of autoregulation may precipitate cerebral ischemia or infarction as a consequence of decreased cerebral blood flow. Renal and coronary blood flows also may decrease with overly aggressive acute therapy. The initial goal of therapy is to reduce mean arterial blood pressure by no more than 25% within minutes to 2 h or to a blood pressure in the range of 160/100–110 mmHg. This may be accomplished with IV nitroprusside, a short-acting vasodilator with a rapid onset of action that allows for minute-to-minute control of blood pressure. Parenteral labetalol and nicardipine are also effective agents for the treatment of hypertensive encephalopathy.

In patients with malignant hypertension without encephalopathy or another catastrophic event, it is preferable to reduce blood pressure over hours or longer rather than minutes. This goal may effectively be achieved initially with frequent dosing of short-acting oral agents such as captopril, clonidine, and labetalol.

Acute, transient blood pressure elevations that last days to weeks frequently occur after thrombotic and hemorrhagic strokes. Autoregulation of cerebral blood flow is impaired in ischemic cerebral tissue, and higher arterial pressures may be required to maintain cerebral blood flow. Although specific blood pressure targets have not been defined for patients with acute cerebrovascular events, aggressive reductions of blood pressure are to be avoided. With the increasing availability of improved methods for measuring cerebral blood flow (using

TABLE 43-10

USUAL INTRAVENOUS DOSES OF ANTIHYPERTENSIVE AGENTS USED IN HYPERTENSIVE EMERGENCIES ^a	
ANTIHYPERTENSIVE AGENT	INTRAVENOUS DOSE
Nitroprusside	Initial 0.3 (μg/kg)/min; usual 2–4 (μg/kg)/min; maximum 10 (μg/kg)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg or 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 μg/kg over 1 min, then 50–300 (μg/kg)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 μg/min, then titrate by 5 μg/min at 3–5-min intervals; if no response is seen at 20 μg/min, incremental increases of 10–20 μg/min may be used
Hydralazine	10–50 mg at 30-min intervals

^aConstant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.

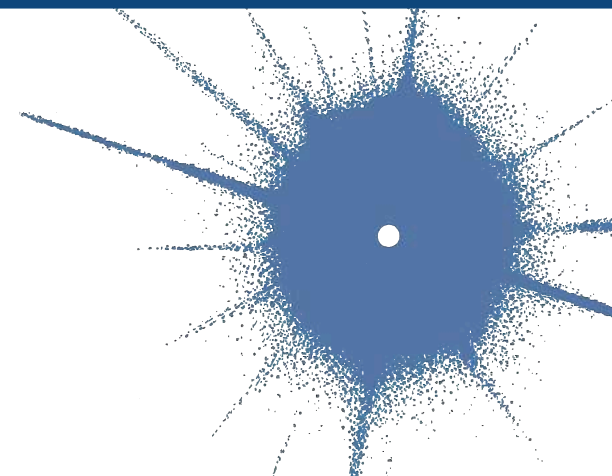
CT technology), studies are in progress to evaluate the effects of different classes of antihypertensive agents on both blood pressure and cerebral blood flow after an acute stroke. Currently, in the absence of other indications for acute therapy, for patients with cerebral infarction who are not candidates for thrombolytic therapy, one recommended guideline is to institute antihypertensive therapy only for patients with a systolic blood pressure >220 mmHg or a diastolic blood pressure >130 mmHg. If thrombolytic therapy is to be used, the recommended goal blood pressure is <185 mmHg systolic pressure and <110 mmHg diastolic pressure. In patients with hemorrhagic stroke, suggested guidelines for initiating antihypertensive therapy are systolic >180 mmHg or diastolic pressure >130 mmHg. The management of hypertension after subarachnoid hemorrhage is controversial. Cautious reduction of blood pressure is indicated if mean arterial pressure is >130 mmHg.

In addition to pheochromocytoma, an adrenergic crisis due to catecholamine excess may be related to cocaine or amphetamine overdose, clonidine withdrawal, acute spinal cord injuries, and an interaction of tyramine-containing compounds with monoamine oxidase inhibitors. These patients may be treated with phentolamine or nitroprusside.

Treatment of hypertension in patients with acute aortic dissection is discussed in Chap. 46.

CHAPTER 44

RENOVASCULAR DISEASE



Stephen C. Textor

The renal vasculature is unusually complex with rich arteriolar flow to the cortex in excess of metabolic requirements, consistent with its primary function as a filtering organ. After delivering blood to cortical glomeruli, the postglomerular circulation supplies deeper medullary segments that support energy-dependent solute transport at multiple levels of the renal tubule. These postglomerular vessels carry less blood, and high oxygen consumption leaves the deeper medullary regions at the margin of hypoxemia. Vascular disorders that commonly threaten the blood supply of the kidney include large-vessel atherosclerosis, fibromuscular diseases, and embolic disorders.

The glomerular capillary endothelium shares susceptibility to oxidative stress, pressure injury, and inflammation with other vascular territories. Rates of urinary albumin excretion (UAE) are predictive of systemic atherosclerotic disease events. Increased UAE may develop years before cardiovascular events. UAE and the risk of cardiovascular events are both reduced with pharmacologic therapy such as statins. Experimental studies demonstrate functional changes and rarefaction of renal microvessels under conditions of accelerated atherosclerosis and/or compromise of proximal perfusion pressures with large-vessel disease (**Fig. 44-1**).

MACROVASCULAR DISEASE

Large-vessel renal artery occlusive disease can result from extrinsic compression of the vessel, fibromuscular dysplasia, or, most commonly, atherosclerotic disease. Any disorder that reduces perfusion pressure to the kidney can activate mechanisms that tend to restore renal pressures at the expense of developing systemic hypertension. Because restoration of perfusion pressures can reverse these pathways, renal artery stenosis is considered a specifically treatable “secondary” cause of hypertension.

Renal artery stenosis is common and often has only minor hemodynamic effects. Fibromuscular dysplasia

(FMD) is reported in 3–5% of normal subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but sometimes produces total occlusion and can be associated with renal artery aneurysms. Atherosclerotic renal artery stenosis (ARAS) is common in the general population (6.8% of a community-based sample above age 65), and the prevalence increases with age and for patients with other vascular conditions such as coronary artery disease (18–23%) and/or peripheral aortic or lower extremity disease (>30%). If untreated, ARAS progresses in nearly 50% of cases over a 5-year period, sometimes to total occlusion. Intensive treatment of arterial blood pressure and statin therapy appear to slow these rates and improve clinical outcomes.

Critical levels of stenosis lead to a reduction in perfusion pressure that activates the renin-angiotensin system, reduces sodium excretion, and activates sympathetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages, widely varying pressures, loss of circadian blood pressure (BP) rhythms, and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. It can also be treated with restoration of renal blood flow by either endovascular or surgical revascularization. Most patients require continued antihypertensive drug therapy because revascularization alone rarely lowers BP to normal.

ARAS and systemic hypertension tend to affect both the post-stenotic and contralateral kidneys, reducing overall glomerular filtration rate (GFR) in ARAS. When kidney function is threatened by large-vessel disease primarily, it has been labeled ischemic nephropathy.

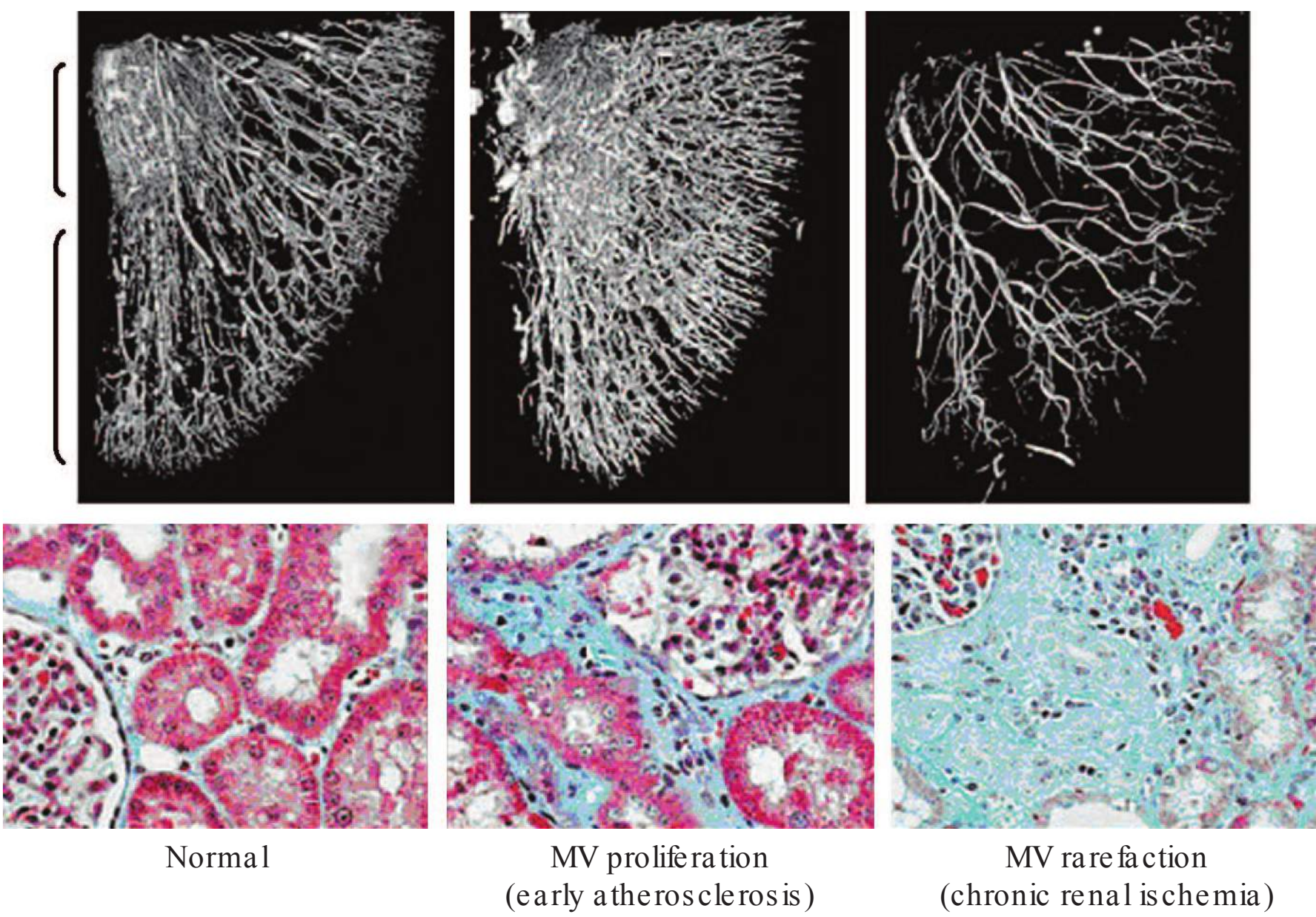


FIGURE 44-1
Examples of micro-CT images from vessels defined by radiopaque casts injected into the renal vasculature. These illustrate the complex, dense cortical capillary network supplying the kidney cortex that can either proliferate or succumb to rarefaction under the influence of atherosclerosis and/or occlusive disease. Changes in blood supply are followed by tubulointerstitial fibrosis and loss of kidney function. MV, microvascular. (From IO Lerman, AR Chade: Curr Opin Nephrol Hyper 18:160, 2009, with permission.)

Moderately reduced blood flow that develops gradually is associated with reduced GFR and limited oxygen consumption with preserved tissue oxygenation. Hence, kidney function can remain stable during medical therapy, sometimes for years. With more advanced disease, reductions in cortical perfusion and frank tissue hypoxia develop. Unlike FMD, ARAS develops in patients with other risk factors for atherosclerosis and is commonly superimposed upon preexisting small-vessel disease in the kidney resulting from hypertension, aging, and diabetes. Nearly 85% of patients considered

for renal revascularization have stage 3–5 chronic kidney disease (CKD) with GFR below 60 mL/min per 1.73 m². The presence of ARAS is a strong predictor of morbidity- and mortality-related cardiovascular events, independent of whether renal revascularization is undertaken.

Diagnostic approaches to renal artery stenosis depend partly on the specific issues to be addressed. Noninvasive characterization of the renal vasculature may be achieved by several techniques, summarized in **Table 44-1**. Although activation of the renin-angiotensin system is

TABLE 44-1

SUMMARY OF IMAGING MODALITIES FOR EVALUATING THE KIDNEY VASCULATURE			
PERFUSION STUDIES TO ASSESS DIFFERENTIAL RENAL BLOOD FLOW			
Captopril renography with technetium ^{99m} Tc mertiatide (^{99m} Tc MAG3)	Captopril-mediated fall in filtration pressure amplifies differences in renal perfusion	Normal study excludes renovascular hypertension	Multiple limitations in patients with advanced atherosclerosis or creatinine >2.0 mg/dL (177 μmol/L)
Vascular Studies to Evaluate the Renal Arteries			
Duplex ultrasonography	Shows the renal arteries and measures flow velocity as a means of assessing the severity of stenosis	Inexpensive; widely available	Heavily dependent on operator's experience; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia and abnormalities in accessory renal arteries
Magnetic resonance angiography	Shows the renal arteries and perirenal aorta	Not nephrotoxic, but concerns for gadolinium toxicity exclude use in GFR <30 mL/min/1.73 m ² ; provides excellent images	Expensive; gadolinium excluded in renal failure, unable to visualize stented vessels
Computed tomographic angiography	Shows the renal arteries and perirenal aorta	Provides excellent images; stents do not cause artifacts	Expensive, moderate volume of contrast required, potentially nephrotoxic
Intraarterial angiography	Shows location and severity of vascular lesion	Considered "gold standard" for diagnosis of large-vessel disease, usually performed simultaneous with planned intervention	Expensive, associated hazard of atheroemboli, contrast toxicity, procedure-related complications, e.g., dissection

Abbreviation: GFR, glomerular filtration rate.

a key step in developing renovascular hypertension, it is transient. Levels of renin activity are therefore subject to timing, the effects of drugs, and sodium intake, and do not reliably predict the response to vascular therapy. Renal artery velocities by Doppler ultrasound above 200 cm/s generally predict hemodynamically important lesions (above 60% vessel lumen occlusion), although treatment trials require velocity above 300 cm/s to avoid false positives. The renal resistive index has predictive value regarding the viability of the kidney. It remains operator- and institution-dependent, however. Captopril-enhanced renography has a strong negative predictive value when entirely normal. Magnetic resonance angiography (MRA) is now less often used, as gadolinium contrast has been associated with nephrogenic systemic fibrosis. Contrast-enhanced computed tomography (CT) with vascular reconstruction provides excellent vascular images and functional assessment, but carries a small risk of contrast toxicity.

TREATMENT

Renal Artery Stenosis

While restoring renal blood flow and perfusion seems intuitively beneficial for high-grade occlusive lesions, revascularization procedures also pose hazards and expense. Patients with FMD are commonly younger females with otherwise normal vessels and a long life expectancy. These patients often respond well to percutaneous renal artery angioplasty. If BP can be controlled to goal levels and kidney function remains stable in patients with ARAS, it may be argued that medical therapy with follow-up for disease progression is equally effective. Prospective trials up to now have failed to identify compelling benefits for interventional procedures regarding short-term results of BP and renal function, and long-term studies regarding cardiovascular outcomes, such as stroke, congestive heart failure, myocardial infarction, and end-stage renal failure, are not yet complete. Medical therapy should include blockade of the renin-angiotensin system, attainment of goal BPs, cessation of tobacco, statins, and aspirin. Renal revascularization is now often reserved for patients failing medical therapy or developing additional complications.

Techniques of renal revascularization are improving. With experienced operators, major complications occur in about 9% of cases, including renal artery dissection, capsular perforation, hemorrhage, and occasional atheroembolic disease. Although not common, atheroembolic disease can be catastrophic and accelerate both hypertension and kidney failure, precisely the events that revascularization is intended to prevent. Although renal blood flow usually can be restored by endovascular stenting, recovery of renal function is limited to about 25% of cases, with no change in 50% and some deterioration evident in others. Patients with rapid loss of kidney function, sometimes

TABLE 44-2

CLINICAL FACTORS FAVORING MEDICAL THERAPY AND REVASCULARIZATION OR SURVEILLANCE FOR RENAL ARTERY STENOSIS

Factors Favoring Medical Therapy and Revascularization for Renal Artery Stenosis
• Progressive decline in GFR during treatment of systemic hypertension • Failure to achieve adequate blood pressure control with optimal medical therapy (medical failure) • Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure • Decline in the GFR during therapy with ACE inhibitors or ARBs • Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular function does not explain a cause
Factors Favoring Medical Therapy and Surveillance of Renal Artery Disease
• Controlled blood pressure with stable renal function (e.g., stable renal insufficiency) • Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound) • Very advanced age and/or limited life expectancy • Extensive comorbidity that make revascularization too risky • High risk for or previous experience with atheroembolic disease • Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., interstitial nephritis, diabetic nephropathy)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate.

associated with antihypertensive drug therapy, or with vascular disease affecting the entire functioning kidney mass are more likely to recover function after restoring blood flow. When hypertension is refractory to effective therapy, revascularization offers real benefits. **Table 44-2** summarizes currently accepted guidelines for considering renal revascularization.

ATHEROEMBOLIC RENAL DISEASE

Emboli to the kidneys arise most frequently as a result of cholesterol crystals breaking free of atherosclerotic vascular plaque and lodging in downstream microvessels. Most clinical atheroembolic events follow angiographic procedures, often of the coronary vessels. It has been argued that nearly all vascular interventional procedures lead to plaque fracture and release of microemboli, but clinical manifestations develop only in a fraction of these. The incidence of clinical atheroemboli has been increasing with more vascular procedures and longer life spans. Atheroembolic renal disease is suspected in more

than 3% of elderly subjects with end-stage renal disease (ESRD) and is likely underdiagnosed. It is more frequent in males with a history of diabetes, hypertension, and ischemic cardiac disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinical cases can be linked to precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy, or trauma. Clinical manifestations of this syndrome commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss, are present in less than half of patients, although cutaneous manifestations including livedo reticularis and localized toe gangrene may be more common. Worsening hypertension and deteriorating kidney function are common, sometimes reaching a malignant phase. Progressive renal failure can occur and require dialytic support. These cases often develop after a stuttering onset over many weeks and have an ominous prognosis. Mortality rate after 1 year reaches 38%, and although some may eventually recover sufficiently to no longer require dialysis, many do not.

Beyond the clinical manifestations above, laboratory findings include rising creatinine, transient eosinophilia (60–80%), elevated sedimentation rate, and hypocomplementemia (15%). Establishing this diagnosis can be difficult and is often by exclusion. Definitive diagnosis depends on kidney biopsy demonstrating microvessel occlusion with cholesterol crystals that leave a “cleft” in the vessel. Biopsies obtained from patients undergoing surgical revascularization of the kidney indicate that silent cholesterol emboli are frequently present before any further manipulation is performed.

No effective therapy is available for atheroembolic disease once it has developed. Withdrawal of anticoagulation is recommended. Late recovery of kidney function after supportive measures sometimes occurs, and statin therapy may improve outcome. The role of embolic protection devices in the renal circulation is unclear, but a few prospective trials have failed to demonstrate major benefits. These devices are limited to distal protection during the endovascular procedure and offer no protection from embolic debris after removal.

THROMBOEMBOLIC RENAL DISEASE

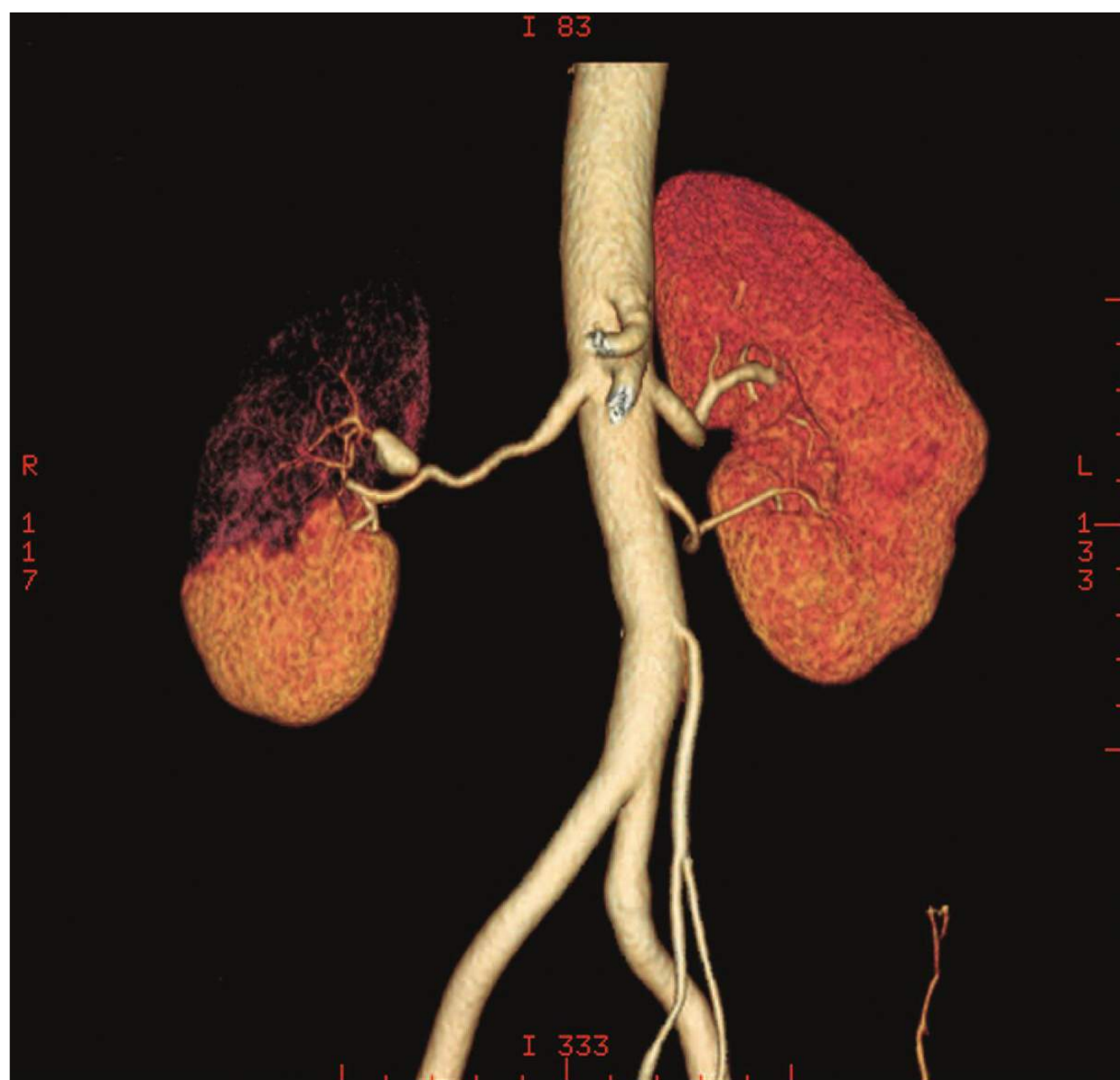
Thrombotic occlusion of renal vessels or branch arteries can lead to declining renal function and

hypertension. It is difficult to diagnose and is often overlooked, especially in elderly patients. Thrombosis can develop as a result of local vessel abnormalities, such as local dissection, trauma, or inflammatory vasculitis. Local microdissections sometimes lead to patchy, transient areas of infarctions labeled “segmental arteriolar mediolysis.” Although hypercoagulability conditions sometimes present as renal artery thrombosis, this is rare. It can also derive from distant embolic events, e.g., the left atrium in patients with atrial fibrillation or from fat emboli originating from traumatized tissue, most commonly large bone fractures. Cardiac sources include vegetations from subacute bacterial endocarditis. Systemic emboli to the kidneys may also arise from the venous circulation if right-to-left shunting occurs, e.g., through a patent foramen ovale.

Clinical manifestations vary depending on the rapidity of onset and extent of occlusion. Acute arterial thrombosis may produce flank pain, fever, leukocytosis, nausea, and vomiting. If kidney infarction results, enzymes such as lactate dehydrogenase (LDH) rise to extreme levels. If both kidneys are affected, renal function will decline precipitously with a drop in urine output. If a single kidney is involved, renal functional changes may be minor. Hypertension related to sudden release of renin from ischemic tissue can develop rapidly, as long as some viable tissue in the “peri-infarct” border zone remains. If the infarct zone demarcates precisely, the rise in BP and renin activity may resolve. Diagnosis of renal infarction may be established by vascular imaging with MRI, CT angiography, or arteriography (Fig. 44-2).

MANAGEMENT OF ARTERIAL THROMBOSIS OF THE KIDNEY

Options for interventions of newly detected arterial occlusion include surgical reconstruction, anticoagulation, thrombolytic therapy, endovascular procedures, and supportive care, particularly antihypertensive drug therapy. Application of these methods depends on the patient's overall condition, the precipitating factors (e.g., local trauma or systemic illness), the magnitude of renal tissue and function at risk, and the likelihood of recurrent events in the future. For unilateral disease, e.g., arterial dissection with thrombosis, supportive care with anticoagulation may suffice. Acute, bilateral occlusion is potentially catastrophic, producing anuric renal failure. Depending on the precipitating event, surgical or thrombolytic therapies can sometimes restore kidney viability.



A

FIGURE 44-2

A. CT angiogram illustrating loss of circulation to the upper pole of the right kidney in a patient with fibromuscular disease and a renal artery aneurysm. Activation of the renin-angiotensin system produced rapidly developing hypertension. B. Angiogram illustrating high-grade renal artery stenosis affecting the left kidney.



B

This lesion is often part of widespread atherosclerosis and sometimes is an extension of aortic plaque. This lesion develops in older individuals with preexisting atherosclerotic risk factors.

MICROVASCULAR INJURY ASSOCIATED WITH HYPERTENSION

ARTERIOLONEPHROSCLEROSIS

“Malignant” hypertension

Although BP rises with age, it has long been recognized that some individuals develop rapidly progressive BP elevations with target organ injury including retinal hemorrhages, encephalopathy, and declining kidney function. Placebo arms during the controlled trials of hypertension therapy identified progression to severe levels in 20% of subjects over 5 years. If untreated, patients with target organ injury including papilledema and declining kidney function suffered mortality rates in excess of 50% over 6–12 months, hence the designation “malignant.” Postmortem studies of such patients identified vascular lesions, designated “fibrinoid necrosis,” with breakdown of the vessel wall, deposition of eosinophilic material including fibrin, and a perivascular cellular infiltrate. A separate lesion was identified in the larger interlobular

arteries in many patients with hyperplastic proliferation of the vascular wall cellular elements, deposition of collagen, and separation of layers, designated the “onionskin” lesion. For many of these patients, fibrinoid necrosis led to obliteration of glomeruli and loss of tubular structures. Progressive kidney failure ensued and, without dialysis support, led to early mortality in untreated malignant-phase hypertension. These vascular changes could develop with pressure-related injury from a variety of hypertensive pathways, including but not limited to activation of the renin-angiotensin system and severe vasospasm associated with catecholamine release. Occasionally, endothelial injury is sufficient to induce microangiopathic hemolysis, as discussed below.

Antihypertensive therapy is the mainstay of therapy for malignant hypertension. With effective BP reduction, manifestations of vascular injury including microangiopathic hemolysis and renal dysfunction can improve over time. Whereas series reported before the era of drug therapy suggested that 1-year mortality rates exceeded 90%, current survival over 5 years exceeds 50%.

Malignant hypertension is less common in Western countries, although it persists in parts of the world where medical care and antihypertensive drug therapy are less available. It most commonly develops in patients with treated hypertension who neglect to take medications or who may use vasospastic drugs, such as cocaine. Renal abnormalities typically include rising serum creatinine and occasionally hematuria and proteinuria. Biochemical findings may include evidence of hemolysis (anemia, schistocytes, and reticulocytosis) and changes associated with kidney failure. African-American males are more likely to develop rapidly progressive hypertension and kidney failure than are whites in the United States. Genetic polymorphisms (first identified as MYH9, but now thought to be APOL1) that are common in the African-American population predispose to subtle focal sclerosing glomerular disease, with severe hypertension developing at younger ages secondary to renal disease in this instance.

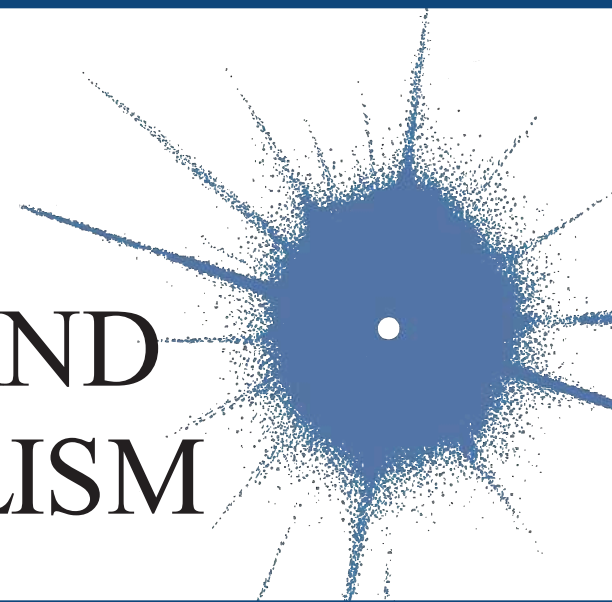
“Hypertensive nephrosclerosis”

Based on experience with malignant hypertension and epidemiologic evidence linking BP with long-term

risks of kidney failure, it has long been assumed that lesser degrees of hypertension induce less severe, but prevalent, changes in kidney vessels and loss of kidney function. As a result, a large portion of patients reaching ESRD without a specific etiologic diagnosis are assigned the designation “hypertensive nephrosclerosis.” Pathologic examination commonly identifies afferent arteriolar thickening with deposition of homogeneous eosinophilic material (hyaline arteriosclerosis) associated with narrowing of vascular lumina. Clinical manifestations include retinal vessel changes associated with hypertension (arteriolar narrowing, crossing changes), left ventricular hypertrophy, and elevated BP. The role of these vascular changes in kidney function is unclear. Postmortem and biopsy samples from normotensive kidney donors demonstrate similar vessel changes associated with aging, dyslipidemia, and glucose intolerance. Although BP reduction does slow progression of proteinuric kidney diseases and is warranted to reduce the excessive cardiovascular risks associated with CKD, antihypertensive therapy does not alter the course of kidney dysfunction identified specifically as hypertensive nephrosclerosis.

CHAPTER 45

DEEP VENOUS THROMBOSIS AND PULMONARY THROMBOEMBOLISM



Samuel Z. Goldhaber

EPIDEMIOLOGY

Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death and disability. In the United States, the Surgeon General estimates there are 100,000 to 180,000 deaths annually from PE and has declared that PE is the most common preventable cause of death among hospitalized patients. Survivors may succumb to the disabilities of chronic thromboembolic pulmonary hypertension or postthrombotic syndrome. Chronic thromboembolic pulmonary hypertension causes breathlessness, especially with exertion. Postthrombotic syndrome (also known as chronic venous insufficiency) damages the venous valves of the leg and causes ankle or calf swelling and leg aching, especially after prolonged standing. In its most severe form, postthrombotic syndrome causes skin ulceration (Fig. 45-1).

PATHOPHYSIOLOGY

Inflammation and platelet activation

Virchow's triad of inflammation, hypercoagulability, and endothelial injury leads to recruitment of activated platelets, which release microparticles. These microparticles contain proinflammatory mediators that bind neutrophils, stimulating them to release their nuclear material and form web-like extracellular networks called neutrophil extracellular traps. These prothrombotic networks contain histones that stimulate platelet aggregation and promote platelet-dependent thrombin generation. Venous thrombi form and flourish in an environment of stasis, low oxygen tension, and upregulation of proinflammatory genes.

Prothrombotic states

The two most common autosomal dominant genetic mutations are factor V Leiden, which causes resistance to the endogenous anticoagulant, activated protein C (which inactivates clotting factors V and VIII), and the prothrombin gene mutation, which increases the plasma prothrombin concentration. Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors. Deficiencies of these inhibitors are associated with VTE but are rare. Antiphospholipid antibody syndrome is the most common acquired cause of thrombophilia and is associated with venous or arterial thrombosis. Other common predisposing factors include cancer, obesity, cigarette smoking, systemic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, blood transfusion, long-haul air travel, air pollution, oral contraceptives, pregnancy, postmenopausal hormone replacement, surgery, and trauma.

Embolization

When deep venous thrombi (Fig. 45-2) detach from their site of formation, they embolize to the vena cava, right atrium, and right ventricle, and lodge in the pulmonary arterial circulation, thereby causing acute PE. Paradoxically, these thrombi occasionally embolize to the arterial circulation through a patent foramen ovale or atrial septal defect. Many patients with PE have no evidence of DVT because the clot has already embolized to the lungs.

Physiology

The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial O₂ tension gradient, which represents the inefficiency of O₂



FIGURE 45-1

Skin ulceration in the lateral malleolus from postthrombotic syndrome of the leg.

transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries.

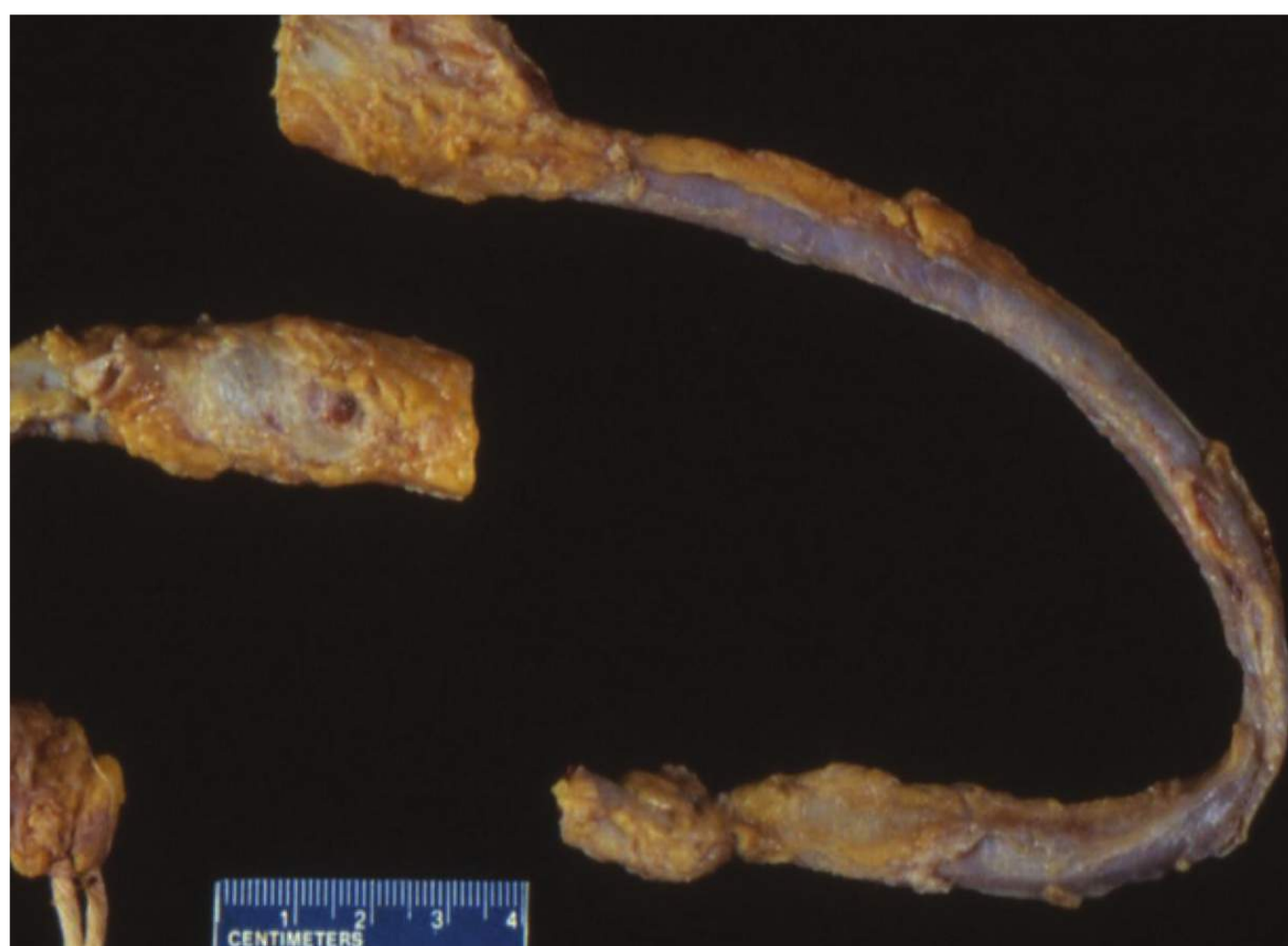


FIGURE 45-2

Deep venous thrombosis at autopsy.

Other pathophysiologic abnormalities include:

1. Increased pulmonary vascular resistance due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin. Release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial O_2 gradient.
2. Impaired gas exchange due to increased alveolar dead space from vascular obstruction, hypoxemia from alveolar hypoventilation relative to perfusion in the nonobstructed lung, right-to-left shunting, or impaired carbon monoxide transfer due to loss of gas exchange surface.
3. Alveolar hyperventilation due to reflex stimulation of irritant receptors.
4. Increased airway resistance due to constriction of airways distal to the bronchi.
5. Decreased pulmonary compliance due to lung edema, lung hemorrhage, or loss of surfactant.

Pulmonary hypertension, right ventricular (RV) dysfunction, and RV microinfarction

Pulmonary artery obstruction causes a rise in pulmonary artery pressure and in pulmonary vascular resistance. When RV wall tension rises, RV dilation and dysfunction ensue, with release of the cardiac biomarker, brain natriuretic peptide. The interventricular septum bulges into and compresses an intrinsically normal left ventricle (LV). Diastolic LV dysfunction reduces LV distensibility and impairs LV filling. Increased RV wall tension also compresses the right coronary artery, limits myocardial oxygen supply, and precipitates right coronary artery ischemia and RV microinfarction, with release of cardiac biomarkers such as troponin. Underfilling of the LV may lead to a fall in LV cardiac output and systemic arterial pressure, with consequent circulatory collapse and death.

CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

Pulmonary embolism

Massive PE accounts for 5–10% of cases, and is characterized by extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure. **Submassive PE** accounts for 20–25% of patients, and is characterized by RV dysfunction despite normal systemic arterial pressure. The combination of right heart

failure and release of cardiac biomarkers indicates an increased likelihood of clinical deterioration. **Low-risk PE** constitutes about 70–75% of cases. These patients have an excellent prognosis.

Deep venous thrombosis

Lower extremity DVT usually begins in the calf and propagates proximally to the popliteal vein, femoral vein, and iliac veins. Leg DVT is about 10 times more common than **upper extremity DVT**, which is often precipitated by placement of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters. The likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase. **Superficial venous thrombosis** usually presents with erythema, tenderness, and a “palpable cord.” Patients are at risk for extension of the thrombosis to the deep venous system.

DIAGNOSIS

Clinical evaluation

PE is known as “the Great Masquerader.” Diagnosis is difficult because symptoms and signs are nonspecific. The most common symptom is unexplained breathlessness. When occult PE occurs concomitantly with overt congestive heart failure or pneumonia, clinical improvement often fails to occur despite standard medical treatment of the concomitant illness. This scenario presents a clinical clue to the possible coexistence of PE.

With DVT, the most common symptom is a cramp or “charley horse” in the lower calf that persists and intensifies over several days. Point score criteria help estimate the clinical likelihood of DVT and PE (**Table 45-1**). Patients with a low-to-moderate likelihood of DVT or PE should undergo initial diagnostic evaluation with d-dimer testing alone (see “Blood Tests”) without obligatory imaging tests (**Fig. 45-3**). However, patients with a high clinical likelihood of VTE should skip d-dimer testing and undergo imaging as the next step in the diagnostic algorithm.

Clinical pearls

Not all leg pain is due to DVT, and not all dyspnea is due to PE (**Table 45-2**). Sudden, severe calf discomfort suggests a ruptured Baker’s cyst. Fever and chills usually herald cellulitis rather than DVT. Physical findings, if present, may consist only of mild palpation discomfort in the lower calf. However, massive DVT often presents with marked thigh swelling, tenderness, and erythema. If the leg is diffusely edematous, DVT is unlikely. More probable is an acute exacerbation of venous insufficiency due to postthrombotic syndrome. Upper extremity venous thrombosis may present with asymmetry in

TABLE 45-1

CLINICAL DECISION RULES

Low Clinical Likelihood of DVT if Point Score is Zero or Less; Moderate Likelihood if Score is 1 To 2; High Likelihood If Score Is 3 Or Greater

CLINICAL VARIABLE	DVT SCORE
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	−2
High Clinical Likelihood of PE if Point Score Exceeds 4	
Clinical Variable	PE Score
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

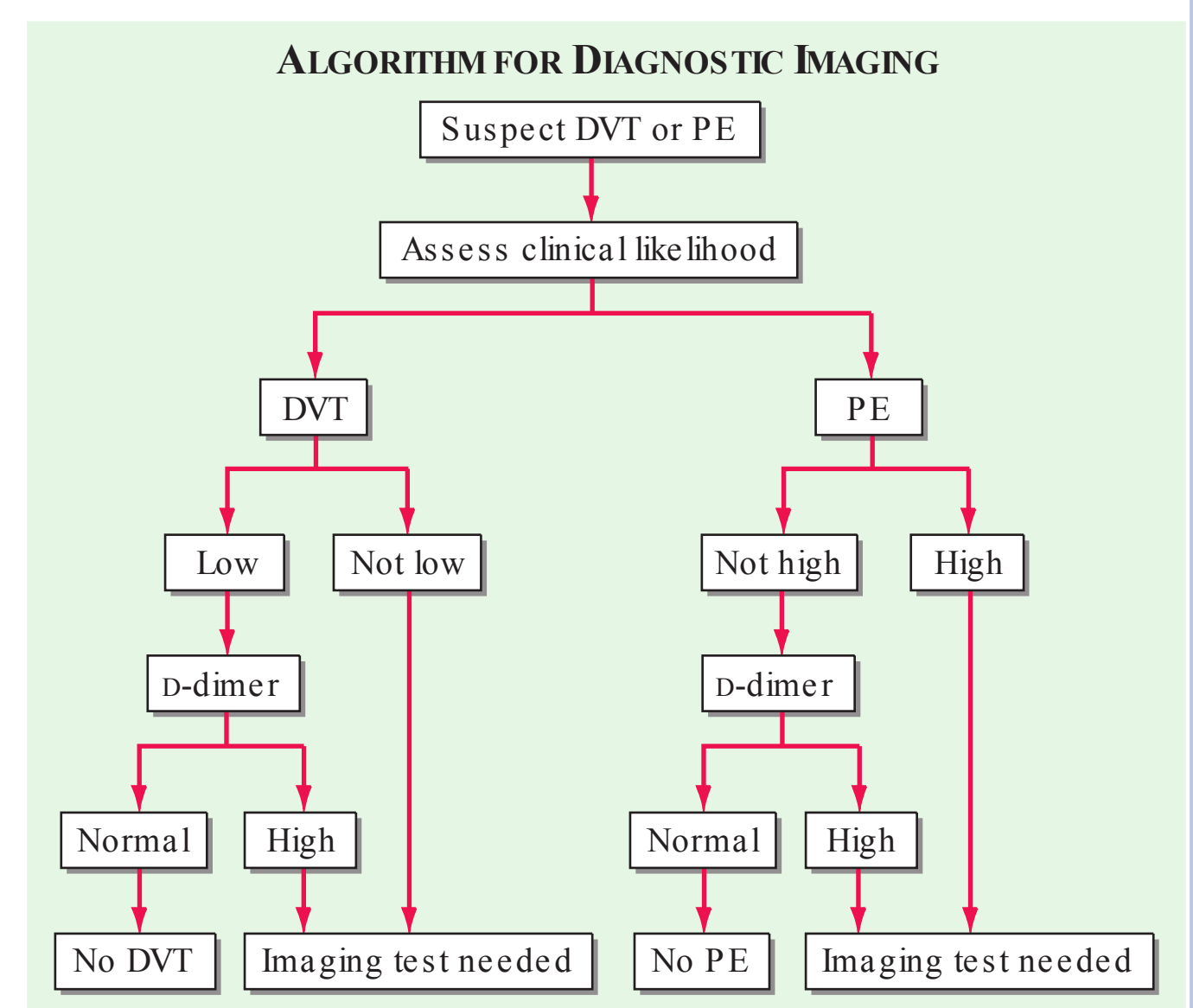


FIGURE 45-3

How to decide whether diagnostic imaging is needed. For assessment of clinical likelihood, see Table 45-1.

TABLE 45-2

DIFFERENTIAL DIAGNOSIS
DVT
Ruptured Baker’s cyst
Cellulitis
Postphlebitic syndrome/venous insufficiency
PE
Pneumonia, asthma, chronic obstructive pulmonary disease
Congestive heart failure
Pericarditis
Pleurisy: “viral syndrome,” costochondritis, musculoskeletal discomfort
Rib fracture, pneumothorax
Acute coronary syndrome
Anxiety

the supraclavicular fossa or in the circumference of the upper arms.

Pulmonary infarction usually indicates a small PE. This condition is exquisitely painful because the thrombus lodges peripherally, near the innervation of pleural nerves. Nonthrombotic PE etiologies include fat embolism after pelvic or long bone fracture, tumor embolism, bone marrow, and air embolism. Cement embolism and bony fragment embolism can occur after total hip or knee replacement. Intravenous drug users may inject themselves with a wide array of substances that can embolize such as hair, talc, and cotton. Amniotic fluid embolism occurs when fetal membranes leak or tear at the placental margin.

Nonimaging diagnostic modalities

Blood tests

The quantitative plasma d-dimer enzyme-linked immunosorbent assay (ELISA) rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin.

Elevation of d-dimer indicates endogenous although often clinically ineffective thrombolysis. The sensitivity of the d-dimer is >80% for DVT (including isolated calf DVT) and >95% for PE. The d-dimer is less sensitive for DVT than for PE because the DVT thrombus size is smaller. A normal d-dimer is a useful “rule out” test. However, the d-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, and the postoperative state and those in the second or third trimester of pregnancy. Therefore, d-dimer rarely has a useful role among hospitalized patients, because levels are frequently elevated due to systemic illness.

Elevated cardiac biomarkers

Serum troponin and plasma heart-type fatty acid-binding protein levels increase because of RV microinfarction. Myocardial stretch causes release of brain natriuretic peptide or NT-pro-brain natriuretic peptide.

Electrocardiogram

The most frequently cited abnormality, in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III (Chap. 11). This finding is relatively specific but insensitive. RV strain and ischemia cause the most common abnormality, T-wave inversion in leads V₁ to V₄.

Noninvasive imaging modalities

Venous ultrasonography

Ultrasonography of the deep venous system relies on loss of vein compressibility as the primary criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure from the ultrasound transducer. This creates the illusion of a “wink.” With acute DVT, the vein loses its compressibility because of passive distention by acute thrombus. The diagnosis of acute DVT is even more secure when thrombus is directly visualized. It appears homogeneous and has low echogenicity (Fig. 45-4). The vein

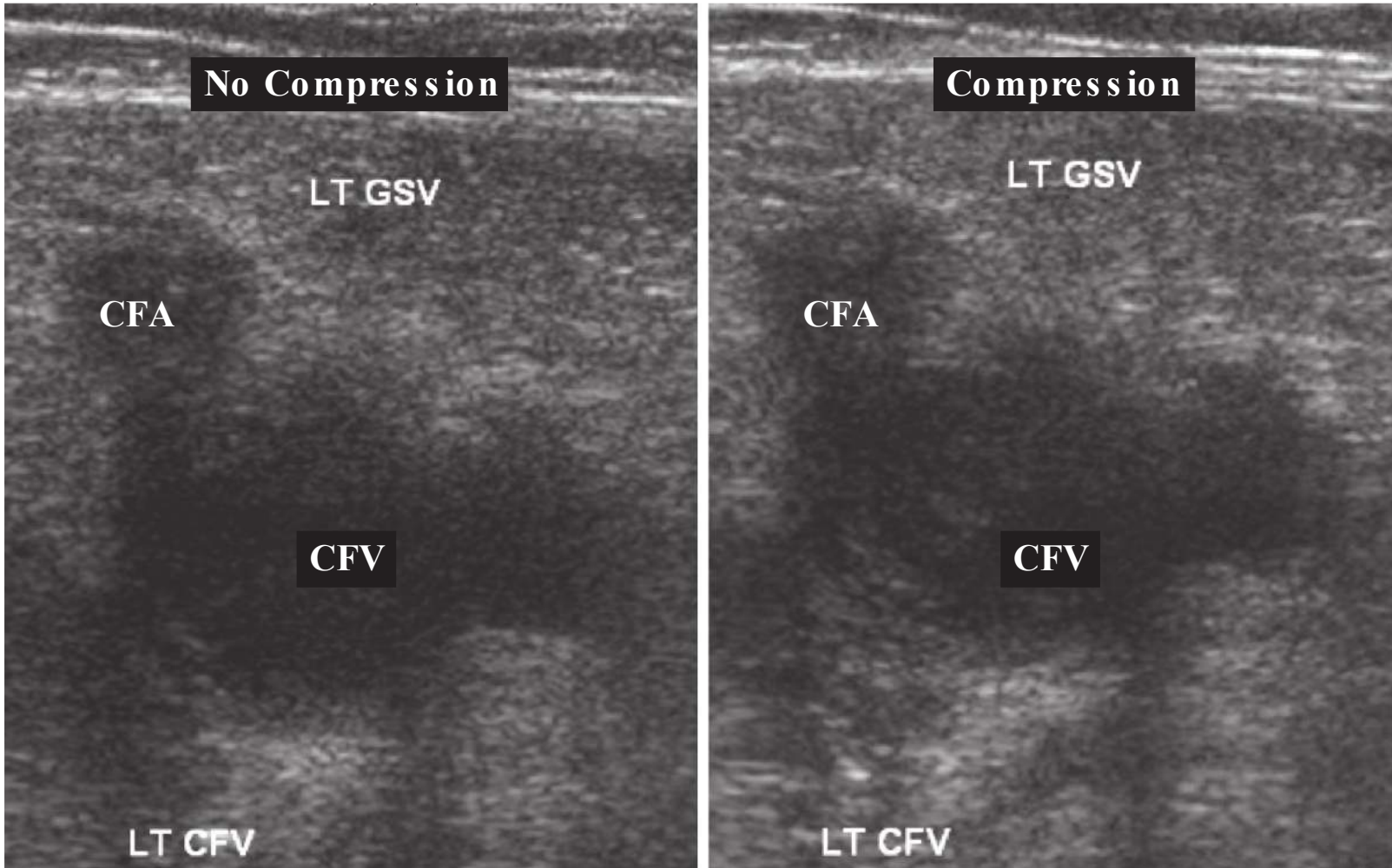


FIGURE 45-4 Venous ultrasound, with and without compression of the leg veins. CFA, common femoral artery; CFV, common femoral vein; GSV, great saphenous vein; LT, left.

itself often appears mildly dilated, and collateral channels may be absent.

Venous flow dynamics can be examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by an obstructing DVT or by any obstructive process within the pelvis. For patients with a technically poor or nondiagnostic venous ultrasound, one should consider alternative imaging modalities for DVT, such as computed tomography (CT) and magnetic resonance imaging.

■ Chest roentgenography

A normal or nearly normal chest x-ray often occurs in PE. Well-established abnormalities include focal oligemia (Westermark's sign), a peripheral wedged-shaped density above the diaphragm (Hampton's hump), and an enlarged right descending pulmonary artery (Palla's sign).

■ Chest CT

CT of the chest with intravenous contrast is the principal imaging test for the diagnosis of PE (**Fig. 45-5**). Multidetector-row spiral CT acquires all chest images with ≤ 1 mm of resolution during a short breath hold. Sixth-order branches can be visualized with resolution superior to that of conventional invasive contrast pulmonary angiography. The CT scan also provides an excellent four-chamber view of the heart. RV enlargement on chest CT indicates an increased likelihood of death within the next 30 days compared with PE

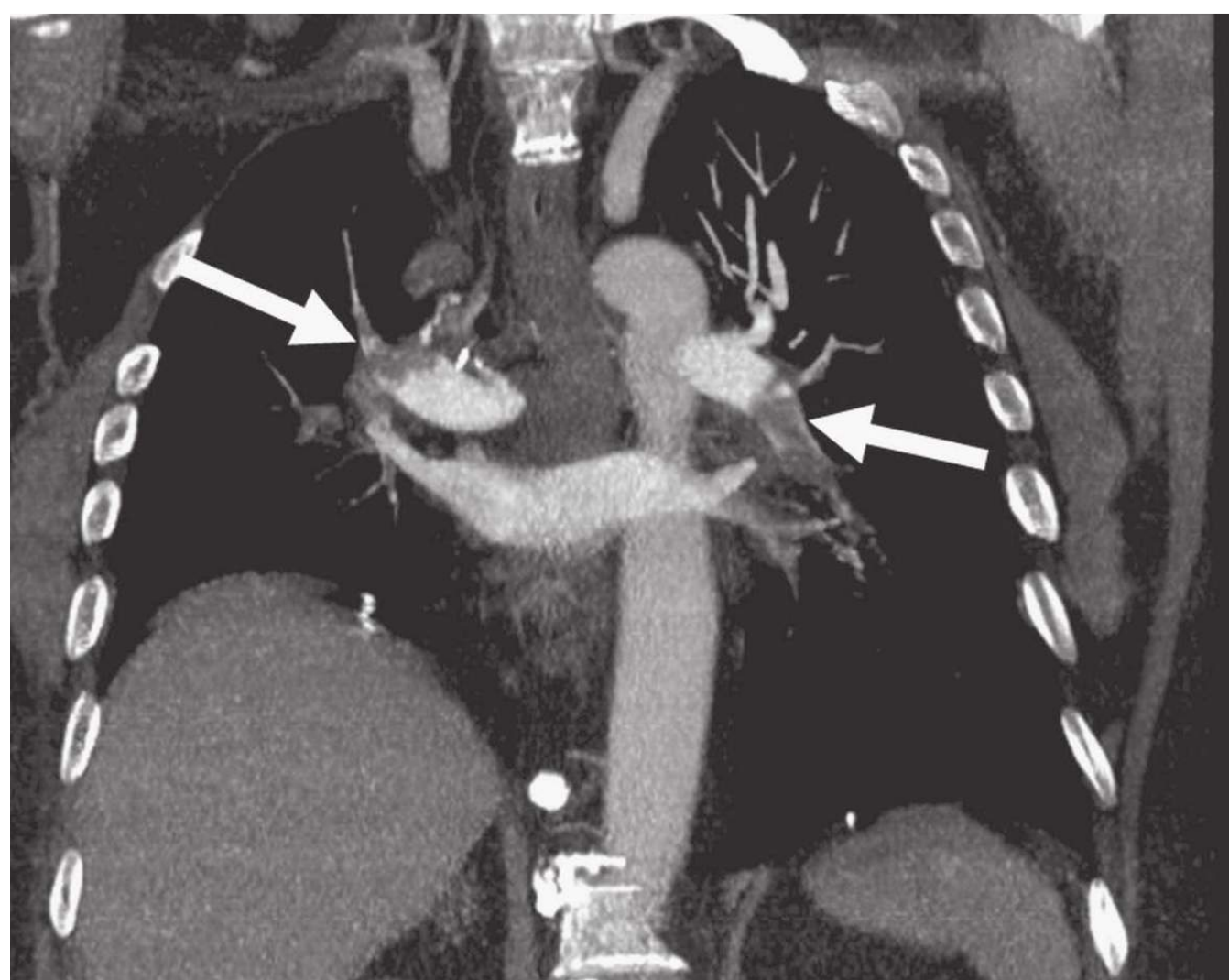


FIGURE 45-5

Large bilateral proximal PE on a coronal chest CT image in a 54-year-old man with lung cancer and brain metastases. He had developed sudden onset of chest heaviness and shortness of breath while at home. There are filling defects in the main and segmental pulmonary arteries bilaterally (white arrows). Only the left upper lobe segmental artery is free of thrombus.

patients who have normal RV size. When imaging is continued below the chest to the knee, pelvic and proximal leg DVT also can be diagnosed by CT scanning. In patients without PE, the lung parenchymal images may establish alternative diagnoses not apparent on chest x-ray that explain the presenting symptoms and signs such as pneumonia, emphysema, pulmonary fibrosis, pulmonary mass, and aortic pathology. Sometimes asymptomatic early-stage lung cancer is diagnosed incidentally.

■ Lung scanning

Lung scanning has become a second-line diagnostic test for PE, used mostly for patients who cannot tolerate intravenous contrast. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected intravenously and are trapped in the pulmonary capillary bed. The perfusion scan defect indicates absent or decreased blood flow, possibly due to PE. Ventilation scans, obtained with a radiolabeled inhaled gas such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal nonventilated lung, thereby providing possible explanations for perfusion defects other than acute PE, such as asthma and chronic obstructive pulmonary disease. A high-probability scan for PE is defined as two or more segmental perfusion defects in the presence of normal ventilation.

The diagnosis of PE is very unlikely in patients with normal and nearly normal scans and is about 90% certain in patients with high-probability scans. Unfortunately, most patients have nondiagnostic scans, and fewer than one-half of patients with angiographically confirmed PE have a high probability scan. As many as 40% of patients with high clinical suspicion for PE but “low-probability” scans do, in fact, have PE at angiography.

■ Magnetic resonance (MR) (contrast-enhanced) imaging

When ultrasound is equivocal, MR venography with gadolinium contrast is an excellent imaging modality to diagnose DVT. MR pulmonary angiography may detect large proximal PE but is not reliable for smaller segmental and subsegmental PE.

■ Echocardiography

Echocardiography is not a reliable diagnostic imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is a very useful diagnostic tool for detecting conditions that may mimic PE, such as acute myocardial infarction, pericardial tamponade, and aortic dissection. Transthoracic echocardiography rarely images thrombus directly. The best-known indirect sign of PE on transthoracic echocardiography is McConnell's sign: hypokinesis of the RV free wall with normal or

532 hyperkinetic motion of the RV apex. One should consider transesophageal echocardiography when CT scanning facilities are not available or when a patient has renal failure or severe contrast allergy that precludes administration of contrast despite premedication with high-dose steroids. This imaging modality can identify saddle, right main, or left main PE.

Invasive diagnostic modalities

Pulmonary angiography

Chest CT with contrast (see above) has virtually replaced invasive pulmonary angiography as a diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs and for those in whom an interventional procedure such as catheter-directed thrombolysis is planned. A definitive diagnosis of PE depends on visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion (“cut-of”) of vessels, segmental oligemia or avascularity, a prolonged arterial phase with slow filling, and tortuous, tapering peripheral vessels.

Contrast phlebography

Venous ultrasonography has virtually replaced contrast phlebography as the diagnostic test for suspected DVT.

Integrated diagnostic approach

An integrated diagnostic approach (Fig. 45-3) streamlines the workup of suspected DVT and PE (Fig. 45-6).

TREATMENT Deep Venous Thrombosis

PRIMARY THERAPY Primary therapy consists of clot dissolution with pharmacomechanical therapy that usually includes low-dose catheter-directed thrombolysis. This approach is reserved for patients with extensive femoral, iliofemoral, or upper extremity DVT. The open vein hypothesis postulates that patients who receive primary therapy will sustain less long-term damage to venous valves, with consequent lower rates of postthrombotic syndrome. A National Heart, Lung, and Blood Institute–sponsored randomized controlled trial called ATTRACT (NCT00790335) is testing this hypothesis.

SECONDARY PREVENTION Anticoagulation or placement of an inferior vena caval filter constitutes secondary prevention of VTE. To lessen the severity of postthrombotic syndrome of the legs, below-knee graduated compression stockings may be prescribed, 30–40 mmHg, for 2 years after the DVT episode. They should be replaced every 3 months because they lose their elasticity.

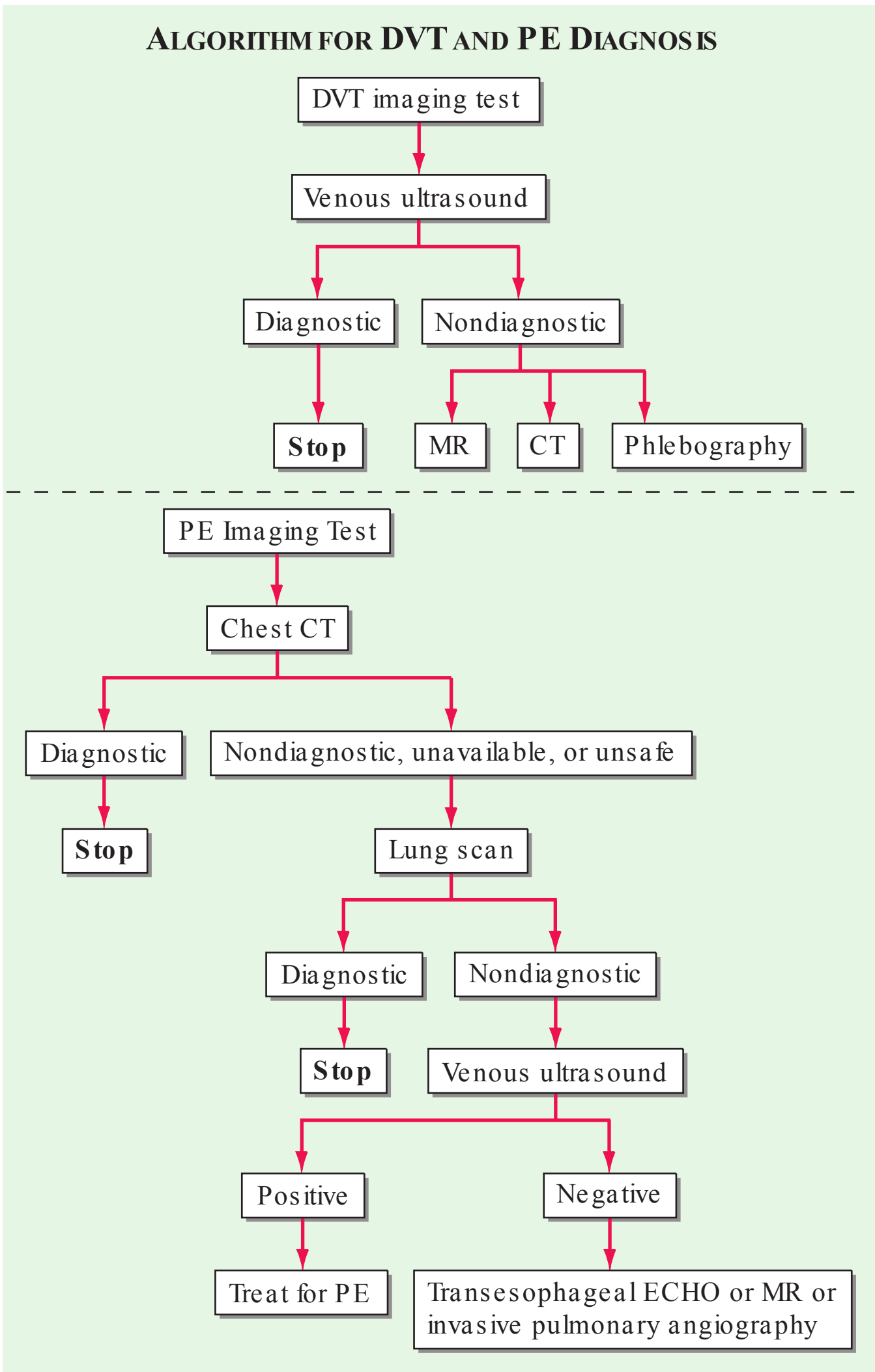


FIGURE 45-6 Imaging tests to diagnose DVT and PE. ECHO, echocardiography.

TREATMENT Pulmonary Embolism

RISK STRATIFICATION Hemodynamic instability, RV dysfunction on echocardiography, RV enlargement on chest CT, or elevation of the troponin level due to RV microinfarction portend a high risk of an adverse clinical outcome. When RV function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone (Fig. 45-7).

ANTICOAGULATION Effective anticoagulation is the foundation for successful treatment of DVT and PE. There are three options: (1) the conventional strategy of parenteral therapy “bridged” to warfarin, (2) parenteral therapy “bridged” to a novel oral anticoagulant such as dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent), or (3) oral anticoagulation with rivaroxaban or apixaban

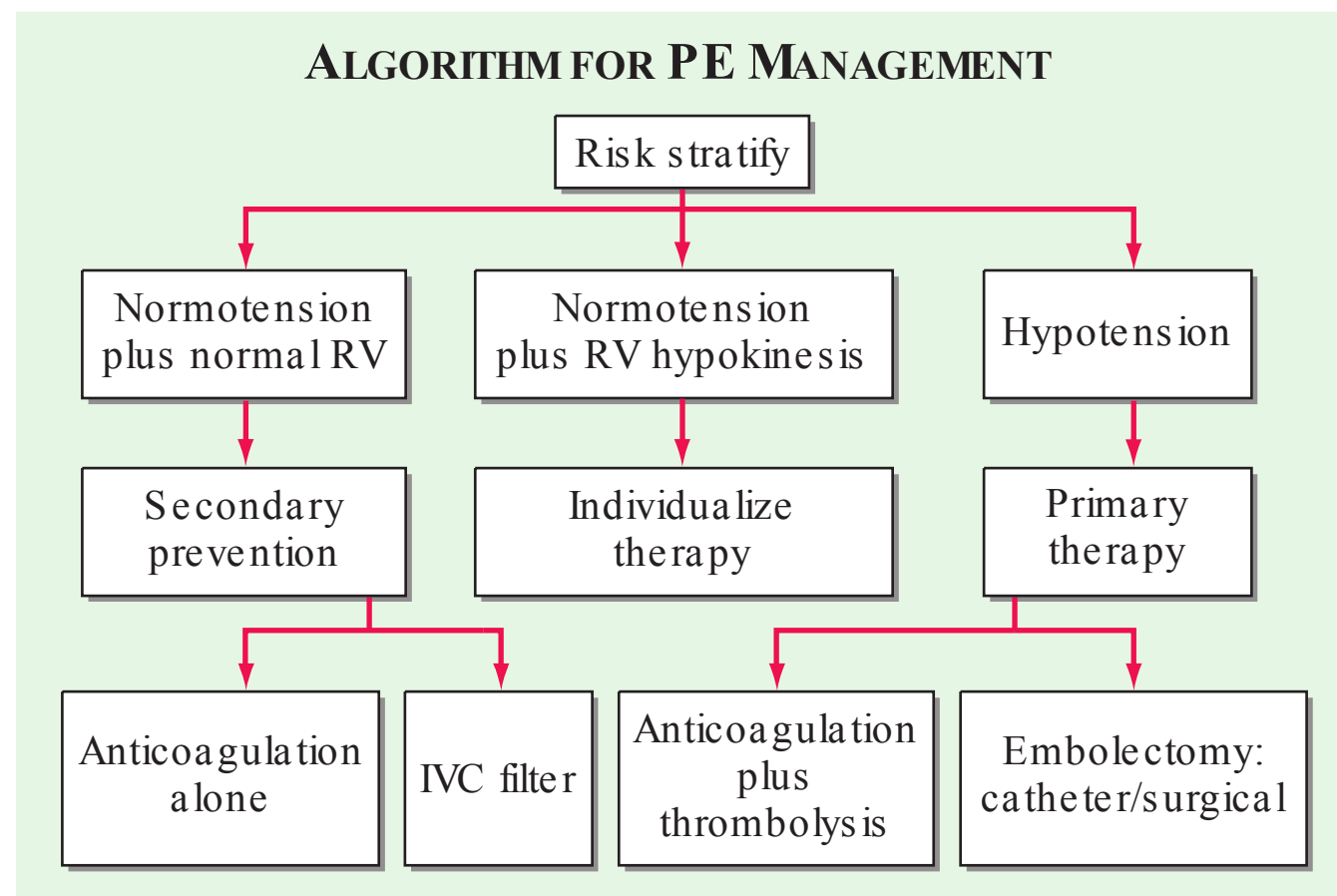


FIGURE 45-7

Acute management of pulmonary thromboembolism. RV, right ventricular; IVC, inferior vena cava.

(both are anti-Xa agents) with a loading dose followed by a maintenance dose as monotherapy without parenteral anticoagulation.

The three heparin-based parenteral anticoagulants are (1) unfractionated heparin (UFH), (2) low-molecular-weight heparin (LMWH), and (3) fondaparinux. For patients with suspected or proven heparin-induced thrombocytopenia, there are two parenteral direct thrombin inhibitors: argatroban and bivalirudin ([Table 45-3](#)).

Unfractionated Heparin UFH anticoagulates by binding to and accelerating the activity of antithrombin, thus preventing additional thrombus formation. UFH is dosed to achieve a target activated partial thromboplastin time (aPTT) of 60–80 s. The most popular nomogram uses an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg per h.

The major advantage of UFH is its short half-life, which is especially useful in patients in whom hour-to-hour control of the intensity of anticoagulation is desired.

Low-Molecular-Weight Heparins These fragments of UFH exhibit less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than does UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease.

Fondaparinux Fondaparinux, an anti-Xa pentasaccharide, is administered as a weight-based once-daily subcutaneous injection in a prefilled syringe. No laboratory monitoring is required. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia. The dose must be adjusted downward for patients with renal dysfunction.

Warfarin This vitamin K antagonist prevents carboxylation activation of coagulation factors II, VII, IX, and X. The full

TABLE 45-3

ANTICOAGULATION OF VTE

Immediate Anticoagulation

Unfractionated heparin, bolus and continuous infusion, to achieve aPTT 2–3 times the upper limit of the laboratory normal, or

Enoxaparin 1 mg/kg twice daily with normal renal function, or

Dalteparin 200 U/kg once daily or 100 U/kg twice daily, with normal renal function, or

Tinzaparin 175 U/kg once daily with normal renal function, or

Fondaparinux weight-based once daily; adjust for impaired renal function

Direct thrombin inhibitors: argatroban or bivalirudin

Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily with the dinner meal thereafter

Apixaban (not yet licensed)

Warfarin Anticoagulation

Requires 5–10 days of administration to achieve effectiveness as monotherapy

(Unfractionated heparin, low-molecular-weight heparin, and fondaparinux are the usual immediately effective “bridging agents” used when initiating warfarin)

Usual start dose is 5 mg

Titrate to INR, target 2.0–3.0

Continue parenteral anticoagulation for a minimum of 5 days and until two sequential INR values, at least 1 day apart, achieve the target INR range

Novel Oral Anticoagulants for Extended-Duration Anticoagulation following Initial Parenteral Anticoagulation

Edoxaban (not yet licensed)

Dabigatran (not yet licensed)

effect of warfarin requires at least 5 days, even if the prothrombin time, used for monitoring, becomes elevated more rapidly. If warfarin is initiated as monotherapy during an acute thrombotic illness, a paradoxical exacerbation of hypercoagulability increases the likelihood of thrombosis. Overlapping UFH, LMWH, fondaparinux, or parenteral direct thrombin inhibitors with warfarin for at least 5 days will nullify the early procoagulant effect of warfarin.

Warfarin Dosing In an average-size adult, warfarin is often initiated in a dose of 5 mg. The prothrombin time is standardized by calculating the international normalized ratio (INR), which assesses the anticoagulant effect of warfarin. The target INR is usually 2.5, with a range of 2.0–3.0.

The warfarin dose is usually titrated empirically to achieve the target INR. Proper dosing is difficult because hundreds of drug-drug and drug-food interactions affect warfarin metabolism. Increasing age and systemic illness reduce the required warfarin dose. Pharmacogenomics may provide more precise initial dosing of warfarin. CYP2C9

variant alleles impair the hydroxylation of S-warfarin, thereby lowering the dose requirement. Variants in the gene encoding the vitamin K epoxide reductase complex 1 (VKORC1) can predict whether patients require low, moderate, or high warfarin doses.

Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Patients can self-monitor their INR with a home point-of-care fingerstick machine and can occasionally be taught to self-dose their warfarin.

Novel Oral Anticoagulants Novel oral anticoagulants are administered in a fixed dose, establish effective anticoagulation within hours of ingestion, require no laboratory coagulation monitoring, and have few of the drug-drug or drug-food interactions that make warfarin so difficult to dose. Rivaroxaban, a factor Xa inhibitor, is approved for treatment of acute DVT and acute PE as monotherapy, without a parenteral “bridging” anticoagulant. Apixaban is likely to receive similar approval for oral monotherapy. Dabigatran, a direct thrombin inhibitor, and edoxaban, a factor Xa inhibitor, are likely to be approved for treatment of VTE after an initial course of parenteral anticoagulation.

Complications of Anticoagulants The most serious adverse effect of anticoagulation is hemorrhage. For life-threatening or intracranial hemorrhage due to heparin or LMWH, protamine sulfate can be administered. Heparin-induced thrombocytopenia is less common with LMWH than with UFH. There is no specific reversal agent for bleeding caused by fondaparinux, direct thrombin inhibitors, or factor Xa inhibitors.

Major bleeding from warfarin is best managed with prothrombin complex concentrate. With serious but non-life-threatening bleeding, fresh-frozen plasma or intravenous vitamin K can be used. Recombinant human coagulation factor VIIa (rFVIIa) is an off-label option to manage catastrophic bleeding from warfarin, but prothrombin complex concentrate is a better choice. Oral vitamin K is effective for managing minor bleeding or an excessively high INR in the absence of bleeding.

Duration of Anticoagulation For DVT isolated to an upper extremity or calf that has been provoked by surgery, trauma, estrogen, or an indwelling central venous catheter or pacemaker, 3 months of anticoagulation usually suffice. For an initial episode of provoked proximal leg DVT or PE, 3 to 6 months of anticoagulation are considered sufficient. For patients with cancer and VTE, prescribe LMWH as monotherapy without warfarin and continue anticoagulation indefinitely unless the patient is rendered cancer-free.

Among patients with idiopathic, unprovoked VTE, the recurrence rate is high after cessation of anticoagulation. VTE that occurs during long-haul air travel is considered unprovoked. Unprovoked VTE may be caused by an

exacerbation of an underlying inflammatory state and can be conceptualized as a chronic illness, with latent periods between flares of recurrent episodes. American College of Chest Physicians (ACCP) guidelines recommend considering anticoagulation for an indefinite duration with a target INR between 2 and 3 for patients with idiopathic VTE. An alternative approach after the first 6 months of anticoagulation is to reduce the intensity of anticoagulation and to lower the target INR range to between 1.5 and 2.

Counterintuitively, the presence of genetic mutations such as heterozygous factor V Leiden and prothrombin gene mutation does not appear to increase the risk of recurrent VTE. However, patients with antiphospholipid antibody syndrome may warrant indefinite-duration anticoagulation, even if the initial VTE was provoked by trauma or surgery.

INFERIOR VENA CAVAL (IVC) FILTERS The two principal indications for insertion of an IVC filter are (1) active bleeding that precludes anticoagulation and (2) recurrent venous thrombosis despite intensive anticoagulation. Prevention of recurrent PE in patients with right heart failure who are not candidates for fibrinolysis and prophylaxis of extremely high-risk patients are “softer” indications for filter placement. The filter itself may fail by permitting the passage of small-to medium-size clots. Large thrombi may embolize to the pulmonary arteries via collateral veins that develop. A more common complication is caval thrombosis with marked bilateral leg swelling.

Paradoxically, by providing a nidus for clot formation, filters increase the DVT rate, even though they usually prevent PE (over the short term). Retrievable filters can now be placed for patients with an anticipated temporary bleeding disorder or for patients at temporary high risk of PE, such as individuals undergoing bariatric surgery who have a prior history of perioperative PE. The filters can be retrieved up to several months after insertion unless thrombus forms and is trapped within the filter. The retrievable filter becomes permanent if it remains in place or if, for technical reasons such as rapid endothelialization, it cannot be removed.

MANAGEMENT OF MASSIVE PE For patients with massive PE and hypotension, replete volume with 500 mL of normal saline. Additional fluid should be infused with extreme caution because excessive fluid administration exacerbates RV wall stress, causes more profound RV ischemia, and worsens LV compliance and filling by causing further interventricular septal shift toward the LV. Dopamine and dobutamine are first-line inotropic agents for treatment of PE-related shock. Maintain a low threshold for initiating these pressors. Often, a “trial-and-error” approach works best; other agents that may be effective include norepinephrine, vasopressin, or phenylephrine.

FIBRINOLYSIS Successful fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE by (1) dissolving much of the anatomically obstructing pulmonary arterial thrombus, (2) preventing the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension, and (3) lysing much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PE.

The preferred fibrinolytic regimen is 100 mg of recombinant tissue plasminogen activator (tPA) administered as a continuous peripheral intravenous infusion over 2 h. The sooner thrombolysis is administered, the more effective it is. However, this approach can be used for at least 14 days after the PE has occurred.

Contraindications to fibrinolysis include intracranial disease, recent surgery, and trauma. The overall major bleeding rate is about 10%, including a 1–3% risk of intracranial hemorrhage. Careful screening of patients for contraindications to fibrinolytic therapy (**Chap. 41**) is the best way to minimize bleeding risk.

The only Food and Drug Administration–approved indication for PE fibrinolysis is massive PE. For patients with submassive PE, who have preserved systolic blood pressure but moderate or severe RV dysfunction, use of fibrinolysis remains controversial. Results of a 1006-patient European multicentered randomized trial of submassive PE, using the thrombolytic agent tenecteplase, were published in 2014. Death or hemodynamic collapse within 7 days of randomization was reduced by 56% in the tenecteplase group. However, hemorrhagic stroke occurred in 2% of tenecteplase patients versus 0.2% in patients who only received heparin.

PHARMACOMECHANICAL CATHETER-DIRECTED THERAPY Many patients have relative contraindications to full-dose thrombolysis. Pharmacomechanical catheter-directed therapy usually combines physical fragmentation or pulverization of thrombus with catheter-directed low-dose thrombolysis. Mechanical techniques include catheter maceration and intentional embolization of clot more distally, suction thrombectomy, rheolytic hydrolysis, and low-energy ultrasound-facilitated thrombolysis. The dose of alteplase can be markedly reduced, usually to a range of 20 to 25 mg instead of the peripheral intravenous systemic dose of 100 mg.

PULMONARY EMBOLIC THERAPY The risk of major hemorrhage with systemically administered fibrinolysis has prompted a renaissance of interest in surgical embolectomy, an operation that had almost become extinct. More rapid referral before the onset of irreversible multisystem organ failure and improved surgical technique have resulted in a high survival rate.

PULMONARY THROMBOENDARTERECTOMY Chronic thromboembolic pulmonary hypertension develops in 2–4% of acute PE patients. Therefore, PE patients who have initial pulmonary

hypertension (usually diagnosed with Doppler echocardiography) should be followed up at about 6 weeks with a repeat echocardiogram to determine whether pulmonary arterial pressure has normalized. Patients impaired by dyspnea due to chronic thromboembolic pulmonary hypertension should be considered for pulmonary thromboendarterectomy, which, if successful, can markedly reduce, and sometimes even cure, pulmonary hypertension (**Chap. 49**). The operation requires median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of hypothermic circulatory arrest. The mortality rate at experienced centers is approximately 5%. Inoperable patients should be managed with pulmonary vasodilator therapy.

EMOTIONAL SUPPORT Patients with VTE may feel overwhelmed when they learn that they are suffering from PE or DVT. Some have never previously encountered serious cardiovascular illness. They wonder whether they will be able to adapt to the new limitations imposed by anticoagulation. They worry about the health of their families and the genetic implications of their illness. Those who are advised to discontinue anticoagulation may feel especially vulnerable about the potential for suffering recurrent VTE. At Brigham and Women's Hospital, a physician-nurse-facilitated PE support group was initiated to address these concerns and has met monthly for more than 20 years.

PREVENTION OF VTE

Prevention of DVT and PE (**Table 45-4**) is of paramount importance because VTE is difficult to detect and poses a profound medical and economic burden. Low-dose UFH or LMWH is the most common form of in-hospital prophylaxis. Computerized reminder systems can increase the use of preventive measures and, at Brigham and Women's Hospital, have reduced the symptomatic VTE rate by more than 40%. Audits of hospitals to ensure that prophylaxis protocols are being used will also increase utilization of preventive measures. Duration of prophylaxis is an important consideration. Extended-duration prophylaxis has not been shown to be both effective and safe in medically ill patients after hospital discharge in separate large trials that have tested enoxaparin, apixaban, and rivaroxaban. There is an ongoing trial of a novel oral anticoagulant, betrixaban, for extended-duration VTE prophylaxis in medically ill patients.

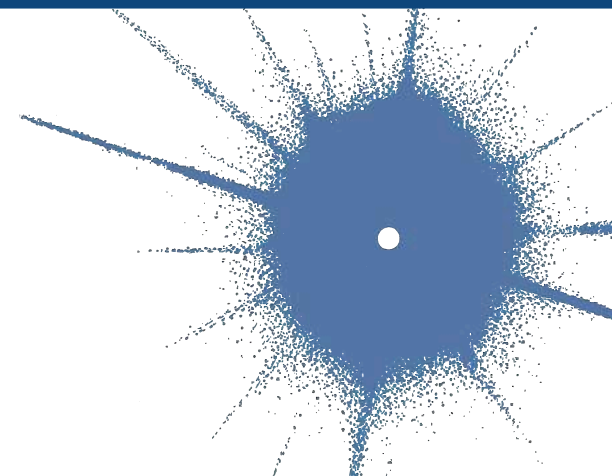
Patients who have undergone total hip or knee replacement or cancer surgery will benefit from extended pharmacologic VTE prophylaxis after hospital discharge. For hip replacement or extensive cancer surgery, the duration of prophylaxis is usually at least 1 month.

TABLE 45-4

PREVENTION OF VENOUS THROMBOEMBOLISM AMONG HOSPITALIZED PATIENTS	
CONDITION	PROPHYLAXIS STRATEGY
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SCbid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Warfarin (target INR2.0–3.0) Enoxaparin 40 mg daily Enoxaparin 30 mg bid Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily Rivaroxaban 10 mg daily Aspirin 81–325 mg daily Dabigatran 220 mg daily (not in the United States) Apixaban 2.5 mg bid (not in the United States) Intermittent pneumatic compression (with or without pharmacologic prophylaxis)
Medically ill patients, especially if immobilized, with a history of prior VTE, with an indwelling central venous catheter, or with cancer (but without active gastroduodenal ulcer, major bleeding within 3 months, or platelet count <50,000)	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Anticoagulation contraindicated	Intermittent pneumatic compression devices (but whether graduated compression stockings are effective in medical patients is controversial)

CHAPTER 46

DISEASES OF THE AORTA



Mark A. Creager ■ Joseph Loscalzo

The aorta is the conduit through which blood ejected from the left ventricle is delivered to the systemic arterial bed. In adults, its diameter is approximately 3 cm at the origin and in the ascending portion, 2.5 cm in the descending portion in the thorax, and 1.8–2 cm in the abdomen. The aortic wall consists of a thin intima composed of endothelium, subendothelial connective tissue, and an internal elastic lamina; a thick tunica media composed of smooth muscle cells and extracellular matrix; and an adventitia composed primarily of connective tissue enclosing the vasa vasorum and nervi vascularis. In addition to the conduit function of the aorta, its viscoelastic and compliant properties serve a buffering function. The aorta is distended during systole to allow a portion of the stroke volume and elastic energy to be stored, and it recoils during diastole so that blood continues to flow to the periphery. Owing to its continuous exposure to high pulsatile pressure and shear stress, the aorta is particularly prone to injury and disease resulting from mechanical trauma. The aorta is also more prone to rupture than is any other vessel, especially with the development of aneurysmal dilation, since its wall tension, as governed by Laplace's law (i.e., proportional to the product of pressure and radius), will be increased.

CONGENITAL ANOMALIES OF THE AORTA

Congenital anomalies of the aorta usually involve the aortic arch and its branches. Symptoms such as dysphagia, stridor, and cough may occur if an anomaly causes a ring around or otherwise compresses the esophagus or trachea. Anomalies associated with symptoms include double aortic arch, origin of the right subclavian artery distal to the left subclavian artery, and right-sided aortic arch with an aberrant left subclavian artery. A Kommerell's diverticulum is an anatomic remnant

of a right aortic arch. Most congenital anomalies of the aorta do not cause symptoms and are detected during catheter-based procedures. The diagnosis of suspected congenital anomalies of the aorta typically is confirmed by computed tomographic (CT) or magnetic resonance (MR) angiography. Surgery is used to treat symptomatic anomalies.

AORTIC ANEURYSM

An aneurysm is defined as a pathologic dilation of a segment of a blood vessel. A true aneurysm involves all three layers of the vessel wall and is distinguished from a pseudoaneurysm, in which the intimal and medial layers are disrupted and the dilated segment of the aorta is lined by adventitia only and, at times, by perivascular clot. Aneurysms also may be classified according to their gross appearance. A fusiform aneurysm affects the entire circumference of a segment of the vessel, resulting in a diffusely dilated artery. In contrast, a saccular aneurysm involves only a portion of the circumference, resulting in an outpouching of the vessel wall. Aortic aneurysms also are classified according to location, i.e., abdominal versus thoracic. Aneurysms of the descending thoracic aorta are usually contiguous with infradiaphragmatic aneurysms and are referred to as thoracoabdominal aortic aneurysms.

ETIOLOGY

Aortic aneurysms result from conditions that cause degradation or abnormal production of the structural components of the aortic wall: elastin and collagen. The causes of aortic aneurysms may be broadly categorized as degenerative disorders, genetic or developmental diseases, vasculitis, infections, and trauma (**Table 46-1**). Inflammation, oxidative stress, proteolysis, and biomechanical wall stress contribute to the degenerative

TABLE 46-1

DISEASES OF THE AORTA: ETIOLOGY AND ASSOCIATED FACTORS	
Aortic aneurysm	
Degenerative	
Aging	
Cigarette smoking	
Hypercholesterolemia	
Hypertension	
Atherosclerosis	
Genetic or developmental	
Marfan's syndrome	
Loeys-Dietz syndrome	
Ehlers-Danlos syndrome type IV	
Turner's syndrome	
Familial	
Bicuspid aortic valve	
Chronic aortic dissection	
Aortitis (see below)	
Infective (see below)	
Trauma	
Acute aortic syndromes (aortic dissection, acute intramural hematoma, penetrating atherosclerotic ulcer)	
Degenerative disorders (see above)	
Genetic/developmental disorders (see above)	
Hypertension	
Aortitis (see below)	
Pregnancy	
Trauma	
Aortic occlusion	
Atherosclerosis	
Thromboembolism	
Aortitis	
Vasculitis	
Takayasu's arteritis	
Giant cell arteritis	
Rheumatic	
HLA-B27-associated spondyloarthropathies	
Behçet's syndrome	
Cogan's syndrome	
Idiopathic aortitis	
Infective	
Syphilis	
Tuberculosis	
Mycotic (Salmonella, staphylococcal, streptococcal, fungal)	

processes that characterize most aneurysms of the abdominal and descending thoracic aorta. These are mediated by B cell and T cell lymphocytes, macrophages, inflammatory cytokines, and matrix metalloproteinases that degrade elastin and collagen and alter the tensile strength and ability of the aorta to accommodate pulsatile stretch. The associated histopathology demonstrates destruction of elastin and collagen, decreased vascular smooth muscle, in-growth of new blood vessels, and inflammation. Factors associated with degenerative aortic aneurysms include aging, cigarette smoking, hypercholesterolemia, hypertension, and male sex.

The most common pathologic condition associated with degenerative aortic aneurysms is atherosclerosis. Many patients with aortic aneurysms have coexisting risk factors for atherosclerosis (**Chap. 36**), as well as atherosclerosis in other blood vessels.

Medial degeneration, previously designated cystic medial necrosis, is the histopathologic term used to describe the degeneration of collagen and elastic fibers in the tunica media of the aorta as well as the loss of medial cells that are replaced by multiple clefts of mucoid material, such as proteoglycans. Medial degeneration characteristically affects the proximal aorta, results in circumferential weakness and dilation, and leads to the development of fusiform aneurysms involving the ascending aorta and the sinuses of Valsalva. This condition is particularly prevalent in patients with Marfan's syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome type IV, hypertension, congenital bicuspid aortic valves, and familial thoracic aortic aneurysm syndromes; sometimes it appears as an isolated condition in patients without any other apparent disease.

Familial clusterings of aortic aneurysms occur in 20% of patients, suggesting a hereditary basis for the disease. Mutations of the gene that encodes fibrillin-1 are present in patients with Marfan's syndrome. Fibrillin-1 is an important component of extracellular microfibrils, which support the architecture of elastic fibers and other connective tissue. Deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by transforming growth factor β (TGF- β). Loeys-Dietz syndrome is caused by mutations in the genes that encode TGF- β receptors 1 (TGFB1) and 2 (TGFB2). Increased signaling by TGF- β and mutations of TGFB1 and TGFB2 may cause thoracic aortic aneurysms. Mutations of type III procollagen have been implicated in Ehlers-Danlos type IV syndrome. Mutations of SMAD3, which encodes a downstream signaling protein involved with TGF binding to its receptors, have been described in a syndrome of thoracic aortic aneurysm; craniofacial, skeletal, and cutaneous anomalies; and osteoarthritis. Mutations of the

genes encoding the smooth muscle–specific alpha-actin (ACTA2), smooth muscle cell–specific myosin heavy chain 11 (MHC11), and myosin light chain kinase (MYLK) and mutations of TGFBR2 and SMAD3 have been reported in some patients with nonsyndromic familial thoracic aortic aneurysms.

The infectious causes of aortic aneurysms include syphilis, tuberculosis, and other bacterial infections. Syphilis is a relatively uncommon cause of aortic aneurysm. Syphilitic periaortitis and mesoaortitis damage elastic fibers, resulting in thickening and weakening of the aortic wall. Approximately 90% of syphilitic aneurysms are located in the ascending aorta or aortic arch. Tuberculous aneurysms typically affect the thoracic aorta and result from direct extension of infection from hilar lymph nodes or contiguous abscesses as well as from bacterial seeding. Loss of aortic wall elasticity results from granulomatous destruction of the medial layer. A mycotic aneurysm is a rare condition that develops as a result of staphylococcal, streptococcal, Salmonella, or other bacterial or fungal infections of the aorta, usually at an atherosclerotic plaque. These aneurysms are usually saccular. Blood cultures are often positive and reveal the nature of the infective agent.

Vasculitides associated with aortic aneurysm include Takayasu's arteritis and giant cell arteritis, which may cause aneurysms of the aortic arch and descending thoracic aorta. Spondyloarthropathies such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, relapsing polychondritis, and reactive arthritis (formerly known as Reiter's syndrome) are associated with dilation of the ascending aorta. Aortic aneurysms occur in patients with Behçet's syndrome, Cogan's syndrome, and IgG4-related systemic disease. Aortic aneurysms also result from idiopathic aortitis. Traumatic aneurysms may occur after penetrating or non-penetrating chest trauma and most commonly affect the descending thoracic aorta just beyond the site of insertion of the ligamentum arteriosum. Chronic aortic dissections are associated with weakening of the aortic wall that may lead to the development of aneurysmal dilatation.

THORACIC AORTIC ANEURYSMS

The clinical manifestations and natural history of thoracic aortic aneurysms depend on their location. Medial degeneration is the most common pathology associated with ascending aortic aneurysms, whereas atherosclerosis is the condition most frequently associated with aneurysms of the descending thoracic aorta. The average growth rate of thoracic aneurysms is 0.1–0.2 cm per year. Thoracic aortic aneurysms associated with Marfan's syndrome or aortic dissection may expand at

a greater rate. The risk of rupture is related to the size of the aneurysm and the presence of symptoms, ranging approximately from 2–3% per year for thoracic aortic aneurysms <4.0 cm in diameter to 7% per year for those >6 cm in diameter. Most thoracic aortic aneurysms are asymptomatic; however, compression or erosion of adjacent tissue by aneurysms may cause symptoms such as chest pain, shortness of breath, cough, hoarseness, and dysphagia. Aneurysmal dilation of the ascending aorta may cause congestive heart failure as a consequence of aortic regurgitation, and compression of the superior vena cava may produce congestion of the head, neck, and upper extremities.

A chest x-ray may be the first test that suggests the diagnosis of a thoracic aortic aneurysm (**Fig. 46-1**). Findings include widening of the mediastinal shadow and displacement or compression of the trachea or left main stem bronchus. Echocardiography, particularly transesophageal echocardiography, can be used to assess the proximal ascending aorta and descending thoracic aorta. Contrast-enhanced CT, magnetic resonance imaging (MRI), and conventional invasive aortography are sensitive and specific tests for assessment of aneurysms of the thoracic aorta and involvement of branch vessels (**Fig. 46-2**). In asymptomatic patients whose aneurysms are too small to justify surgery, non-invasive testing with either contrast-enhanced CT or MRI should be performed at least every 6–12 months to monitor expansion.



FIGURE 46-1

A chest x-ray of a patient with a thoracic aortic aneurysm.

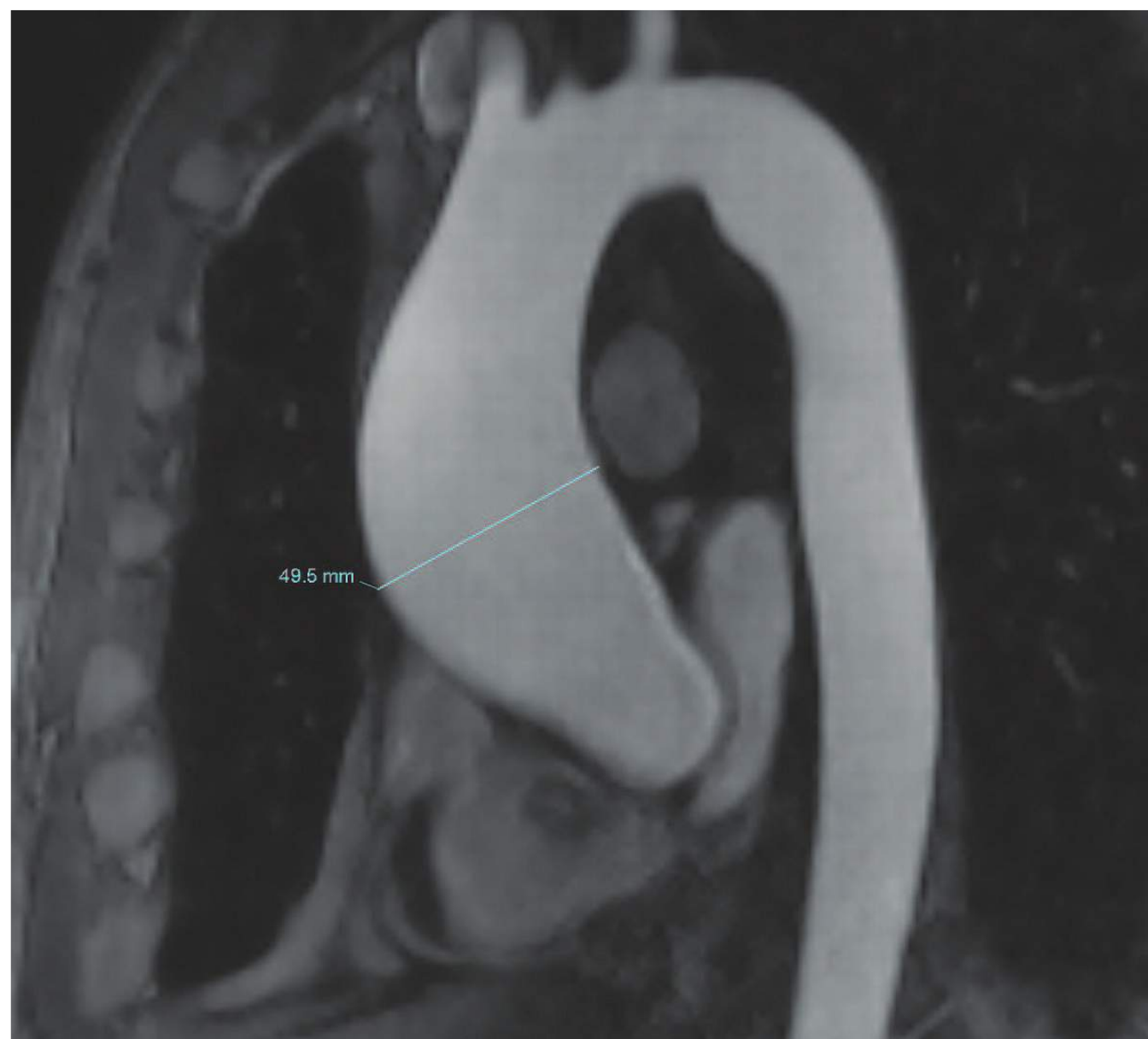


FIGURE 46-2

A magnetic resonance angiogram demonstrating a fusiform aneurysm of the ascending thoracic aorta. (Courtesy of Dr. Michael Steigner, Brigham and Women's Hospital, Boston, MA, with permission.)

TREATMENT Thoracic Aortic Aneurysms

β -Adrenergic blockers currently are recommended for patients with thoracic aortic aneurysms, particularly those with Marfan's syndrome, who have evidence of aortic root dilatation to reduce the rate of further expansion. Additional medical therapy should be given as necessary to control hypertension. Recent studies indicate that angiotensin receptor antagonists and angiotensin-converting enzyme inhibitors reduce the rate of aortic dilation in patients with Marfan's syndrome by blocking TGF- β signaling; clinical outcome trials of this treatment approach are in progress. Operative repair with placement of a prosthetic graft is indicated in patients with symptomatic ascending thoracic aortic aneurysms and for most asymptomatic aneurysms when the ascending aortic diameter is >5.5 cm. In patients with Marfan's syndrome or bicuspid aortic valve, ascending thoracic aortic aneurysms of 4–5 cm should be considered for surgery. Operative repair is indicated for patients with descending thoracic aortic aneurysms when the diameter is >6 cm, and endovascular repair should be considered if feasible when the diameter is >5.5 cm. Repair is also recommended when the diameter of an aneurysm has increased >1 cm per year.

ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms occur more frequently in males than in females, and the incidence increases with age. Abdominal aortic aneurysms ≥ 4.0 cm may affect

1–2% of men older than 50 years. At least 90% of all abdominal aortic aneurysms >4.0 cm are related to atherosclerotic disease, and most of these aneurysms are below the level of the renal arteries. Prognosis is related to both the size of the aneurysm and the severity of coexisting coronary artery and cerebrovascular disease. The risk of rupture increases with the size of the aneurysm: the 5-year risk for aneurysms <5 cm is 1–2%, whereas it is 20–40% for aneurysms >5 cm in diameter. The formation of mural thrombi within aneurysms may predispose to peripheral embolization.

An abdominal aortic aneurysm commonly produces no symptoms. It usually is detected on routine examination as a palpable, pulsatile, expansile, and nontender mass, or it is an incidental finding observed on an abdominal imaging study performed for other reasons. As abdominal aortic aneurysms expand, however, they may become painful. Some patients complain of strong pulsations in the abdomen; others experience pain in the chest, lower back, or scrotum. Aneurysmal pain is usually a harbinger of rupture and represents a medical emergency. More often, acute rupture occurs without any prior warning, and this complication is always life-threatening. Rarely, there is leakage of the aneurysm with severe pain and tenderness. Acute pain and hypotension occur with rupture of the aneurysm, which requires an emergency operation.

Abdominal radiography may demonstrate the calcified outline of the aneurysm; however, about 25% of aneurysms are not calcified and cannot be visualized by x-ray imaging. An abdominal ultrasound can delineate the transverse and longitudinal dimensions of an abdominal aortic aneurysm and may detect mural thrombus. Abdominal ultrasound is useful for serial documentation of aneurysm size and can be used to screen patients at risk for developing an aortic aneurysm. In one large study, ultrasound screening of men age 65–74 years was associated with a risk reduction in aneurysm-related death of 42%. For this reason, screening by ultrasonography is recommended for men age 65–75 years who have ever smoked. In addition, siblings or offspring of persons with abdominal aortic aneurysms, as well as individuals with thoracic aortic or peripheral arterial aneurysms, should be considered for screening for abdominal aortic aneurysms. CT with contrast and MRI are accurate noninvasive tests to determine the location and size of abdominal aortic aneurysms and to plan endovascular or open surgical repair (**Fig. 46-3**). Contrast aortography may be used for the evaluation of patients with aneurysms, but the procedure carries a small risk of complications such as bleeding, allergic reactions, and atheroembolism. Since the presence of mural thrombi may reduce the luminal size, aortography may underestimate the diameter of an aneurysm.



FIGURE 46-3

A computed tomographic angiogram depicting a fusiform abdominal aortic aneurysm before (left) and after (right) treatment with a bifurcated stent graft. (Courtesy of Drs. Elizabeth George and Frank Rybicki, Brigham and Women's Hospital, Boston, MA, with permission.)

TREATMENT Abdominal Aortic Aneurysms

Operative repair of the aneurysm with insertion of a prosthetic graft or endovascular placement of an aortic stent graft (Fig. 46-3) is indicated for abdominal aortic aneurysms of any size that are expanding rapidly or are associated with symptoms. For asymptomatic aneurysms, abdominal aortic aneurysm repair is indicated if the diameter is >5.5 cm. In randomized trials of patients with abdominal aortic aneurysms <5.5 cm, there was no difference in the long-term (5- to 8-year) mortality rate between those followed with ultrasound surveillance and those undergoing elective surgical repair. Thus, serial noninvasive follow-up of smaller aneurysms (<5 cm) is an alternative to immediate repair. The decision to perform an open surgical operation or endovascular repair is based in part on the vascular anatomy and comorbid conditions. Endovascular repair of abdominal aortic aneurysms has a lower short-term morbidity rate but a comparable long-term mortality rate with open surgical reconstruction. Long-term surveillance with CT or MR aortography is indicated after endovascular repair to detect leaks and possible aneurysm expansion.

In surgical candidates, careful preoperative cardiac and general medical evaluations (followed by appropriate therapy for complicating conditions) are essential. Preexisting coronary artery disease, congestive heart failure, pulmonary disease, diabetes mellitus, and advanced age add to the risk of surgery. β -Adrenergic blockers decrease perioperative cardiovascular morbidity and mortality. With careful preoperative

cardiac evaluation and postoperative care, the operative mortality rate approximates 1–2%. After acute rupture, the mortality rate of emergent operation is 45–50%. Endovascular repair with stent placement is an alternative approach to treat ruptured aneurysms and may be associated with a lower mortality rate.

ACUTE AORTIC SYNDROMES

The four major acute aortic syndromes are aortic rupture (discussed earlier), aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer. Aortic dissection is caused by a circumferential or, less frequently, transverse tear of the intima. It often occurs along the right lateral wall of the ascending aorta where the hydraulic shear stress is high. Another common site is the descending thoracic aorta just below the ligamentum arteriosum. The initiating event is either a primary intimal tear with secondary dissection into the media or a medial hemorrhage that dissects into and disrupts the intima. The pulsatile aortic flow then dissects along the elastic lamellar plates of the aorta and creates a false lumen. The dissection usually propagates distally down the descending aorta and into its major branches, but it may propagate proximally. Distal propagation may be limited by atherosclerotic plaque. In some cases, a secondary distal intimal disruption occurs, resulting in the reentry of blood from the false to the true lumen.

There are at least two important pathologic and radiologic variants of aortic dissection: intramural hematoma without an intimal flap and penetrating atherosclerotic ulcer. Acute intramural hematoma is thought to result from rupture of the vasa vasorum with hemorrhage into the wall of the aorta. Most of these hematomas occur in the descending thoracic aorta. Acute intramural hematomas may progress to dissection and rupture. Penetrating atherosclerotic ulcers are caused by erosion of a plaque into the aortic media, are usually localized, and are not associated with extensive propagation. They are found primarily in the middle and distal portions of the descending thoracic aorta and are associated with extensive atherosclerotic disease. The ulcer can erode beyond the internal elastic lamina, leading to medial hematoma, and may progress to false aneurysm formation or rupture.

Several classification schemes have been developed for thoracic aortic dissections. DeBakey and colleagues initially classified aortic dissections as type I, in which an intimal tear occurs in the ascending aorta but involves the descending aorta as well; type II, in which the dissection is limited to the ascending aorta; and type III, in which the intimal tear is located in the descending aorta with distal propagation of the dissection (**Fig. 46-4**). Another classification (Stanford) is that of type A, in which the dissection involves the ascending aorta (proximal dissection), and type B, in which it is limited to the arch and/or descending aorta (distal dissection). From a management standpoint, classification of aortic dissections and intramural hematomas into type A or B is more practical and useful, since DeBakey types I and II are managed in a similar manner.

The factors that predispose to aortic dissection include those associated with medial degeneration and others that increase aortic wall stress (Table 46-1). Systemic hypertension is a coexisting condition in 70% of patients. Aortic dissection is the major cause of morbidity and mortality in patients with Marfan's syndrome or Loeys-Dietz syndrome, and similarly may affect patients with Ehlers-Danlos syndrome. The incidence also is increased in patients with inflammatory aortitis (i.e., Takayasu's arteritis, giant cell arteritis), congenital aortic valve anomalies (e.g., bicuspid valve), coarctation of the aorta, and a history of aortic trauma. In addition, the risk of dissection is increased in otherwise normal women during the third trimester of pregnancy. Aortic dissection also may occur as a consequence of weight lifting, cocaine use, or deceleration injury.

CLINICAL MANIFESTATIONS

The peak incidence of aortic dissection is in the sixth and seventh decades. Men are more affected than women by a ratio of 2:1. The presentations of aortic

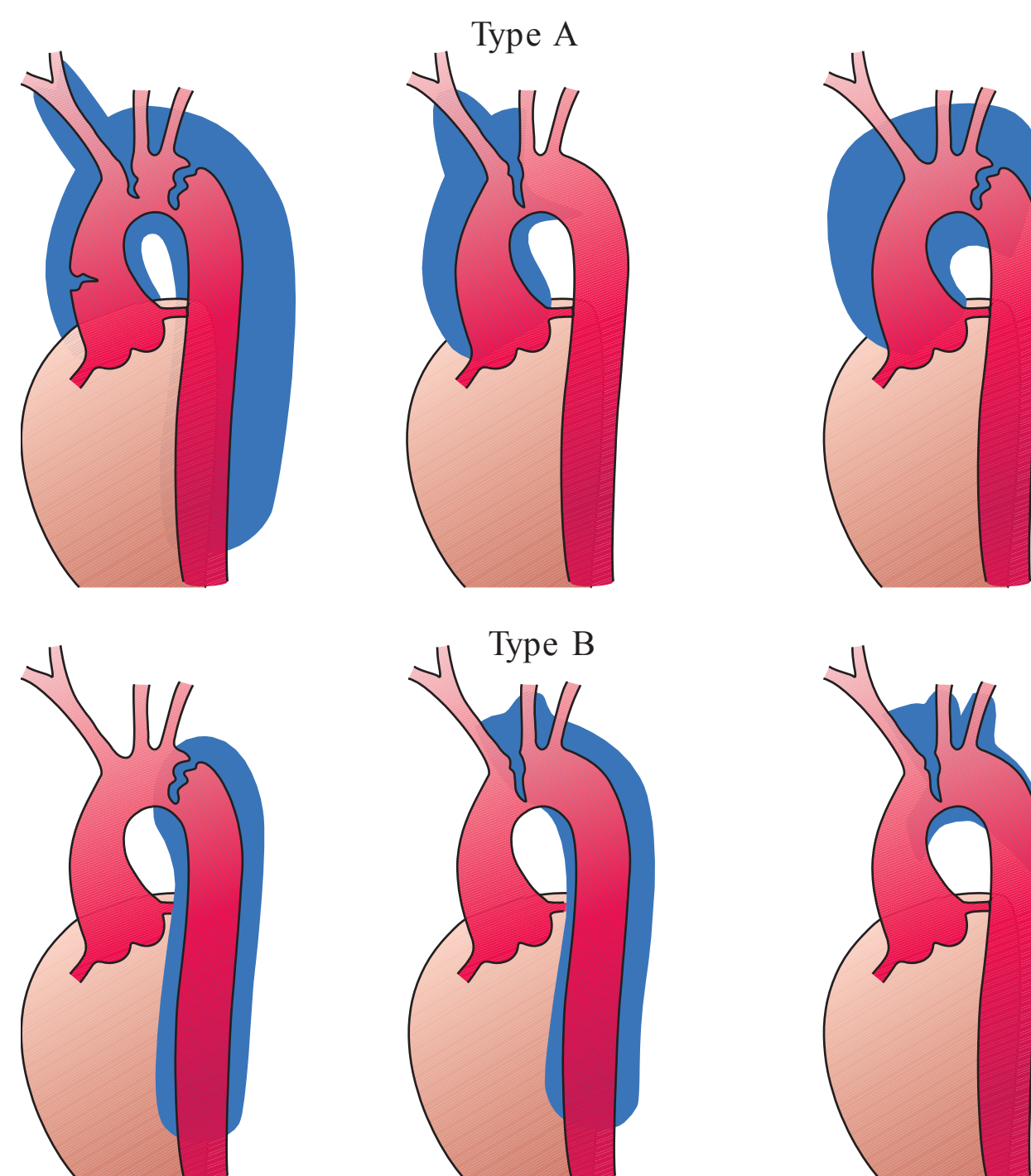


FIGURE 46-4

Classification of aortic dissections. Stanford classification: Type A dissections (top) involve the ascending aorta independent of site of tear and distal extension; type B dissections (bottom) involve transverse and/or descending aorta without involvement of the ascending aorta. DeBakey classification: Type I dissection involves ascending to descending aorta (top left); type II dissection is limited to ascending or transverse aorta, without descending aorta (top center + top right); type III dissection involves descending aorta only (bottom left). (From DC Miller, in RM Doroghazi, EE Slater [eds]: *Aortic Dissection*. New York, McGraw-Hill, 1983, with permission.)

dissection and its variants are the consequences of intimal tear, dissecting hematoma, occlusion of involved arteries, and compression of adjacent tissues. Acute aortic dissection presents with the sudden onset of pain (**Chap. 4**), which often is described as very severe and tearing and is associated with diaphoresis. The pain may be localized to the front or back of the chest, often the interscapular region, and typically migrates with propagation of the dissection. Other symptoms include syncope, dyspnea, and weakness. Physical findings may include hypertension or hypotension, loss of pulses, aortic regurgitation, pulmonary edema, and neurologic findings due to carotid artery obstruction (hemiplegia, hemianesthesia) or spinal cord ischemia (paraplegia). Bowel ischemia, hematuria, and myocardial ischemia have all been observed. These clinical manifestations reflect complications resulting from the dissection occluding the major arteries. Furthermore, clinical manifestations may result from the compression of adjacent structures (e.g., superior cervical

ganglia, superior vena cava, bronchus, esophagus) by the expanding dissection, causing aneurysmal dilation, and include Horner's syndrome, superior vena cava syndrome, hoarseness, dysphagia, and airway compromise. Hemopericardium and cardiac tamponade may complicate a type A lesion with retrograde dissection. Acute aortic regurgitation is an important and common (>50%) complication of proximal dissection. It is the outcome of either a circumferential tear that widens the aortic root or a disruption of the annulus by a dissecting hematoma that tears a leaflet(s) or displaces it, inferior to the line of closure. Signs of aortic regurgitation include bounding pulses, a wide pulse pressure, a diastolic murmur often radiating along the right sternal border, and evidence of congestive heart failure. The clinical manifestations depend on the severity of the regurgitation.

In dissections involving the ascending aorta, the chest x-ray often reveals a widened superior mediastinum. A pleural effusion (usually left-sided) also may be present. This effusion is typically serosanguineous and not indicative of rupture unless accompanied by hypotension and falling hematocrit. In dissections of the descending thoracic aorta, a widened mediastinum may be observed on chest x-ray. In addition, the descending aorta may appear to be wider than the ascending portion. An electrocardiogram that shows no evidence of myocardial ischemia is helpful in distinguishing aortic dissection from myocardial infarction. Rarely, the dissection involves the right or, less commonly, left coronary ostium and causes acute myocardial infarction.

The diagnosis of aortic dissection can be established by noninvasive techniques such as echocardiography, CT, and MRI. Aortography is used less commonly because of the accuracy of these noninvasive techniques. Transthoracic echocardiography can be performed simply and rapidly and has an overall sensitivity of 60–85% for aortic dissection. For diagnosing proximal ascending aortic dissections, its sensitivity exceeds 80%; it is less useful for detecting dissection of the arch and descending thoracic aorta. Transesophageal echocardiography requires greater skill and patient cooperation but is very accurate in identifying dissections of the ascending and descending thoracic aorta but not the arch, achieving 98% sensitivity and approximately 90% specificity. Echocardiography also provides important information regarding the presence and severity of aortic regurgitation and pericardial effusion. CT and MRI are both highly accurate in identifying the intimal flap and the extent of the dissection and involvement of major arteries; each has a sensitivity and specificity >90%. They are useful in recognizing intramural hemorrhage and penetrating ulcers. The relative utility of transesophageal echocardiography, CT, and MRI depends on the availability and expertise in individual

institutions as well as on the hemodynamic stability of the patient, with CT and MRI obviously less suitable for unstable patients.

TREATMENT Aortic Dissection

Medical therapy should be initiated as soon as the diagnosis is considered. The patient should be admitted to an intensive care unit for hemodynamic monitoring. Unless hypotension is present, therapy should be aimed at reducing cardiac contractility and systemic arterial pressure, and thus shear stress. For acute dissection, unless contraindicated, β -adrenergic blockers should be administered parenterally, using intravenous propranolol, metoprolol, or the short-acting esmolol to achieve a heart rate of approximately 60 beats/min. This should be accompanied by sodium nitroprusside infusion to lower systolic blood pressure to ≤ 120 mmHg. Labetalol (**Chap. 43**), a drug with both β - and α -adrenergic blocking properties, also may be used as a parenteral agent in acute therapy for dissection.

The calcium channel antagonists verapamil and diltiazem may be used intravenously if nitroprusside or β -adrenergic blockers cannot be employed. The addition of a parenteral angiotensin-converting enzyme (ACE) inhibitor such as enalaprilat to a β -adrenergic blocker also may be considered. Isolated use of a direct vasodilator such as hydralazine is contraindicated because these agents can increase hydraulic shear and may propagate the dissection.

Emergent or urgent surgical correction is the preferred treatment for acute ascending aortic dissections and intramural hematomas (type A) and for complicated type B dissections, including those characterized by propagation, compromise of major aortic branches, impending rupture, or continued pain. Surgery involves excision of the intimal flap, obliteration of the false lumen, and placement of an interposition graft. A composite valve-graft conduit is used if the aortic valve is disrupted. The overall in-hospital mortality rate after surgical treatment of patients with aortic dissection is reported to be 15–25%. The major causes of perioperative mortality and morbidity include myocardial infarction, paraplegia, renal failure, tamponade, hemorrhage, and sepsis. Endoluminal stent grafts may be considered in selected patients. Other transcatheter techniques, such as fenestration of the intimal flaps and stenting of narrowed branch vessels to increase flow to compromised organs, are used in selected patients. For uncomplicated and stable distal dissections and intramural hematomas (type B), medical therapy is the preferred treatment. The in-hospital mortality rate of medically treated patients with type B dissection is 10–20%. Long-term therapy for patients with aortic dissection and intramural hematomas (with or without surgery) consists of control of hypertension and reduction of cardiac contractility with the use of beta blockers plus other antihypertensive agents, such as ACE inhibitors or calcium antagonists. Patients with

chronic type B dissection and intramural hematomas should be followed on an outpatient basis every 6–12 months with contrast-enhanced CT or MRI to detect propagation or expansion. Patients with Marfan's syndrome are at high risk for postdissection complications. The long-term prognosis for patients with treated dissections is generally good with careful follow-up; the 10-year survival rate is approximately 60%.

CHRONIC ATHEROSCLEROTIC OCCLUSIVE DISEASE

Atherosclerosis may affect the thoracic and abdominal aorta. Occlusive aortic disease caused by atherosclerosis usually is confined to the distal abdominal aorta below the renal arteries. Frequently the disease extends to the iliac arteries (**Chap. 47**). Claudication characteristically involves the buttocks, thighs, and calves and may be associated with impotence in males (Leriche's syndrome). The severity of the symptoms depends on the adequacy of collaterals. With sufficient collateral blood flow, a complete occlusion of the abdominal aorta may occur without the development of ischemic symptoms. The physical findings include the absence of femoral and other distal pulses bilaterally and the detection of an audible bruit over the abdomen (usually at or below the umbilicus) and the common femoral arteries. Atrophic skin, loss of hair, and coolness of the lower extremities usually are observed. In advanced ischemia, rubor on dependency and pallor on elevation can be seen.

The diagnosis usually is established by physical examination and noninvasive testing, including leg pressure measurements, Doppler velocity analysis, pulse volume recordings, and duplex ultrasonography. The anatomy may be defined by MRI, CT, or conventional aortography, typically performed when one is considering revascularization. Catheter-based endovascular or operative treatment is indicated in patients with lifestyle-limiting or debilitating symptoms of claudication and patients with critical limb ischemia.

ACUTE AORTIC OCCLUSION

Acute occlusion in the distal abdominal aorta constitutes a medical emergency because it threatens the viability of the lower extremities; it usually results from an occlusive (saddle) embolus that almost always originates from the heart. Rarely, acute occlusion may occur as the result of in situ thrombosis in a preexisting severely narrowed segment of the aorta.

The clinical picture is one of acute ischemia of the lower extremities. Severe rest pain, coolness, and pallor of the lower extremities and the absence of distal pulses bilaterally are the usual manifestations. Diagnosis should be established rapidly by MRI, CT, or aortography. Emergency thrombectomy or revascularization is indicated.

AORTITIS

Aortitis, a term referring to inflammatory disease of the aorta, may be caused by large vessel vasculitides such as Takayasu's arteritis and giant cell arteritis, rheumatic and HLA-B27-associated spondyloarthropathies, Behçet's syndrome, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, Cogan's syndrome, IgG4-related systemic disease, and infections such as syphilis, tuberculosis, and Salmonella, or may be associated with retroperitoneal fibrosis. Aortitis may result in aneurysmal dilation and aortic regurgitation, occlusion of the aorta and its branch vessels, or acute aortic syndromes.

TAKAYASU'S ARTERITIS

This inflammatory disease often affects the ascending aorta and aortic arch, causing obstruction of the aorta and its major arteries. Takayasu's arteritis is also termed pulseless disease because of the frequent occlusion of the large arteries originating from the aorta. It also may involve the descending thoracic and abdominal aorta and occlude large branches such as the renal arteries. Aortic aneurysms also may occur. The pathology is a panarteritis characterized by mononuclear cells and occasionally giant cells, with marked intimal hyperplasia, medial and adventitial thickening, and, in the chronic form, fibrotic occlusion. The disease is most prevalent in young females of Asian descent but does occur in women of other geographic and ethnic origins and also in young men. During the acute stage, fever, malaise, weight loss, and other systemic symptoms may be evident. Elevations of the erythrocyte sedimentation rate and C-reactive protein are common. The chronic stages of the disease, which is intermittently active, present with symptoms related to large artery occlusion, such as upper extremity claudication, cerebral ischemia, and syncope. The process is progressive, and there is no definitive therapy. Glucocorticoids and immunosuppressive agents are effective in some patients during the acute phase. Surgical bypass or endovascular intervention of a critically stenotic artery may be necessary.

GIANT CELL ARTERITIS

This vasculitis occurs in older individuals and affects women more often than men. Primarily large and medium-size arteries are affected. The pathology is that of focal granulomatous lesions involving the entire arterial wall; it may be associated with polymyalgia rheumatica. Obstruction of medium-size arteries (e.g., temporal and ophthalmic arteries) and major branches of the aorta and the development of aortitis and aortic

regurgitation are important complications of the disease. High-dose glucocorticoid therapy may be effective when given early.

RHEUMATIC AORTITIS

Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis (formerly known as Reiter's syndrome), relapsing polychondritis, and inflammatory bowel disorders may all be associated with aortitis involving the ascending aorta. The inflammatory lesions usually involve the ascending aorta and may extend to the sinuses of Valsalva, the mitral valve leaflets, and adjacent myocardium. The clinical manifestations are aneurysm, aortic regurgitation, and involvement of the cardiac conduction system.

IDIOPATHIC AORTITIS

Idiopathic abdominal aortitis is characterized by adventitial and periaortic inflammation with thickening of the aortic wall. It is associated with abdominal aortic aneurysms and idiopathic retroperitoneal fibrosis. Affected individuals may present with vague constitutional symptoms, fever, and abdominal pain. Retroperitoneal fibrosis can cause ureteral obstruction and hydronephrosis. Glucocorticoids and immunosuppressive agents may reduce the inflammation.

INFECTIVE AORTITIS

Infective aortitis may result from direct invasion of the aortic wall by bacterial pathogens such as *Staphylococcus*, *Streptococcus*, and *Salmonella* or by fungi. These bacteria cause aortitis by infecting the aorta at sites of atherosclerotic plaque. Bacterial proteases lead to degradation of collagen, and the ensuing destruction of the aortic wall leads to the formation of a saccular aneurysm referred to as a mycotic aneurysm. Mycotic aneurysms have a predilection for the suprarenal abdominal aorta. The pathologic characteristics of the aortic wall

include acute and chronic inflammation, abscesses, hemorrhage, and necrosis. Mycotic aneurysms typically affect the elderly and occur in men three times more frequently than in women. Patients may present with fever, sepsis, and chest, back, or abdominal pain; there may have been a preceding diarrheal illness. Blood cultures are positive in the majority of patients. Both CT and MRI are useful to diagnose mycotic aneurysms. Treatment includes antibiotic therapy and surgical removal of the affected part of the aorta and revascularization of the lower extremities with grafts placed in uninfected tissue.

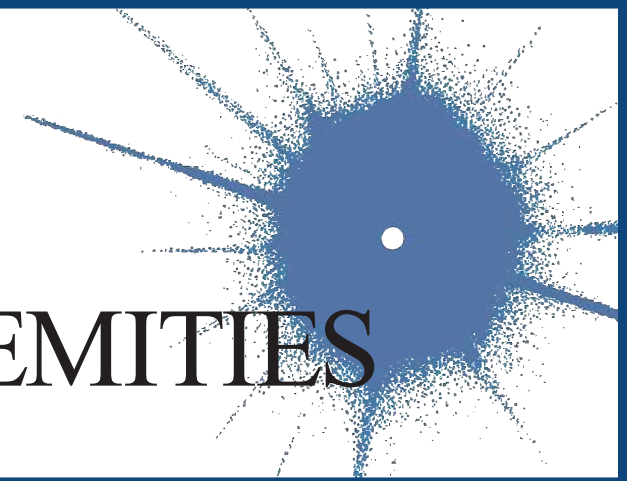
Syphilitic aortitis is a late manifestation of luetic infection that usually affects the proximal ascending aorta, particularly the aortic root, resulting in aortic dilation and aneurysm formation. Syphilitic aortitis occasionally may involve the aortic arch or the descending aorta. The aneurysms may be saccular or fusiform and are usually asymptomatic, but compression of and erosion into adjacent structures may result in symptoms; rupture also may occur.

The initial lesion is an obliterative endarteritis of the vasa vasorum, especially in the adventitia. This is an inflammatory response to the invasion of the adventitia by the spirochetes. Destruction of the aortic media occurs as the spirochetes spread into this layer, usually via the lymphatics accompanying the vasa vasorum. Destruction of collagen and elastic tissues leads to dilation of the aorta, scar formation, and calcification. These changes account for the characteristic radiographic appearance of linear calcification of the ascending aorta.

The disease typically presents as an incidental chest radiographic finding 15–30 years after initial infection. Symptoms may result from aortic regurgitation, narrowing of coronary ostia due to syphilitic aortitis, compression of adjacent structures (e.g., esophagus), or rupture. Diagnosis is established by a positive serologic test, i.e., rapid plasmin reagin (RPR) or fluorescent treponemal antibody. Treatment includes penicillin and surgical excision and repair.

CHAPTER 47

ARTERIAL DISEASES OF THE EXTREMITIES



A. Creager Mark ■ Loscalzo Joseph

PERIPHERAL ARTERY DISEASE

Peripheral artery disease (PAD) is defined as a clinical disorder in which there is a stenosis or occlusion in the aorta or the arteries of the limbs. Atherosclerosis is the leading cause of PAD in patients >40 years old. Other causes include thrombosis, embolism, vasculitis, fibromuscular dysplasia, entrapment, cystic adventitial disease, and trauma. The highest prevalence of atherosclerotic PAD occurs in the sixth and seventh decades of life. As in patients with atherosclerosis of the coronary and cerebral vasculature, there is an increased risk of developing PAD in cigarette smokers and in persons with diabetes mellitus, hypercholesterolemia, hypertension, or renal insufficiency.

Pathology

(See also Chap. 36) Segmental lesions that cause stenosis or occlusion are usually localized to large and medium-size vessels. The pathology of the lesions includes atherosclerotic plaques with calcium deposition, thinning of the media, patchy destruction of muscle and elastic fibers, fragmentation of the internal elastic lamina, and thrombi composed of platelets and fibrin. The primary sites of involvement are the abdominal aorta and iliac arteries (30% of symptomatic patients), the femoral and popliteal arteries (80–90% of patients), and the more distal vessels, including the tibial and peroneal arteries (40–50% of patients). Atherosclerotic lesions occur preferentially at arterial branch points, which are sites of increased turbulence, altered shear stress, and intimal injury. Involvement of the distal vasculature is most common in elderly individuals and patients with diabetes mellitus.

Clinical evaluation

Fewer than 50% of patients with PAD are symptomatic, although many have a slow or impaired gait. The

most common symptom is intermittent claudication, which is defined as a pain, ache, cramp, numbness, or a sense of fatigue in the muscles; it occurs during exercise and is relieved by rest. The site of claudication is distal to the location of the occlusive lesion. For example, buttock, hip, thigh, and calf discomfort occurs in patients with aortoiliac disease, whereas calf claudication develops in patients with femoral-popliteal disease. Symptoms are far more common in the lower than in the upper extremities because of the higher incidence of obstructive lesions in the former region. In patients with severe arterial occlusive disease in whom resting blood flow cannot accommodate basal nutritional needs of the tissues, critical limb ischemia may develop. Patients complain of rest pain or a feeling of cold or numbness in the foot and toes. Frequently, these symptoms occur at night when the legs are horizontal and improve when the legs are in a dependent position. With severe ischemia, rest pain may be persistent.

Important physical findings of PAD include decreased or absent pulses distal to the obstruction, the presence of bruits over the narrowed artery, and muscle atrophy. With more severe disease, hair loss, thickened nails, smooth and shiny skin, reduced skin temperature, and pallor or cyanosis are common physical signs. In patients with critical limb ischemia, ulcers or gangrene may occur. Elevation of the legs and repeated flexing of the calf muscles produce pallor of the soles of the feet, whereas rubor, secondary to reactive hyperemia, may develop when the legs are dependent. The time required for rubor to develop or for the veins in the foot to fill when the patient's legs are transferred from an elevated to a dependent position is related to the severity of the ischemia and the presence of collateral vessels. Patients with severe ischemia may develop peripheral edema because they keep their legs in a dependent position much of the time. Ischemic neuropathy can result in numbness and hyporeflexia.

Noninvasive testing

The history and physical examination are often sufficient to establish the diagnosis of PAD. An objective assessment of the presence and severity of disease is obtained by noninvasive techniques. Arterial pressure can be recorded noninvasively in the legs by placement of sphygmomanometric cuffs at the ankles and the use of a Doppler device to auscultate or record blood flow from the dorsalis pedis and posterior tibial arteries. Normally, systolic blood pressure in the legs and arms is similar. Indeed, ankle pressure may be slightly higher than arm pressure due to pulse-wave amplification. In the presence of hemodynamically significant stenoses, the systolic blood pressure in the leg is decreased. Thus, the ratio of the ankle and brachial artery pressures (termed the ankle:brachial index, or ABI) is 1.00–1.40 in normal individuals. ABI values of 0.91–0.99 are considered “borderline,” and those <0.90 are abnormal and diagnostic of PAD. ABIs >1.40 indicate noncompressible arteries secondary to vascular calcification.

Other noninvasive tests include segmental pressure measurements, segmental pulse volume recordings, duplex ultrasonography (which combines B-mode imaging and Doppler flow velocity waveform analysis examination), transcutaneous oximetry, and stress testing (usually using a treadmill). Placement of pneumatic cuffs enables assessment of systolic pressure along the legs. The presence of pressure gradients between sequential cuffs provides evidence of the presence and

location of hemodynamically significant stenoses. In addition, the amplitude of the pulse volume contour becomes blunted in the presence of significant PAD. Duplex ultrasonography is used to image and detect stenotic lesions in native arteries and bypass grafts.

Treadmill testing allows the physician to assess functional limitations objectively. Decline of the ABI immediately after exercise provides further support for the diagnosis of PAD in patients with equivocal symptoms and findings on examination.

Magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and conventional catheter-based angiography should not be used for routine diagnostic testing but are performed before potential revascularization (**Fig. 47-1**). Each test is useful in defining the anatomy to assist planning for endovascular and surgical revascularization procedures.

Prognosis

The natural history of patients with PAD is influenced primarily by the extent of coexisting coronary artery and cerebrovascular disease. Approximately one-third to one-half of patients with symptomatic PAD have evidence of coronary artery disease (CAD) based on clinical presentation and electrocardiogram, and over one-half have significant CAD by coronary angiography. Patients with PAD have a 15–30% 5-year mortality rate and a two- to sixfold increased risk of death from coronary heart disease. Mortality rates are highest in those

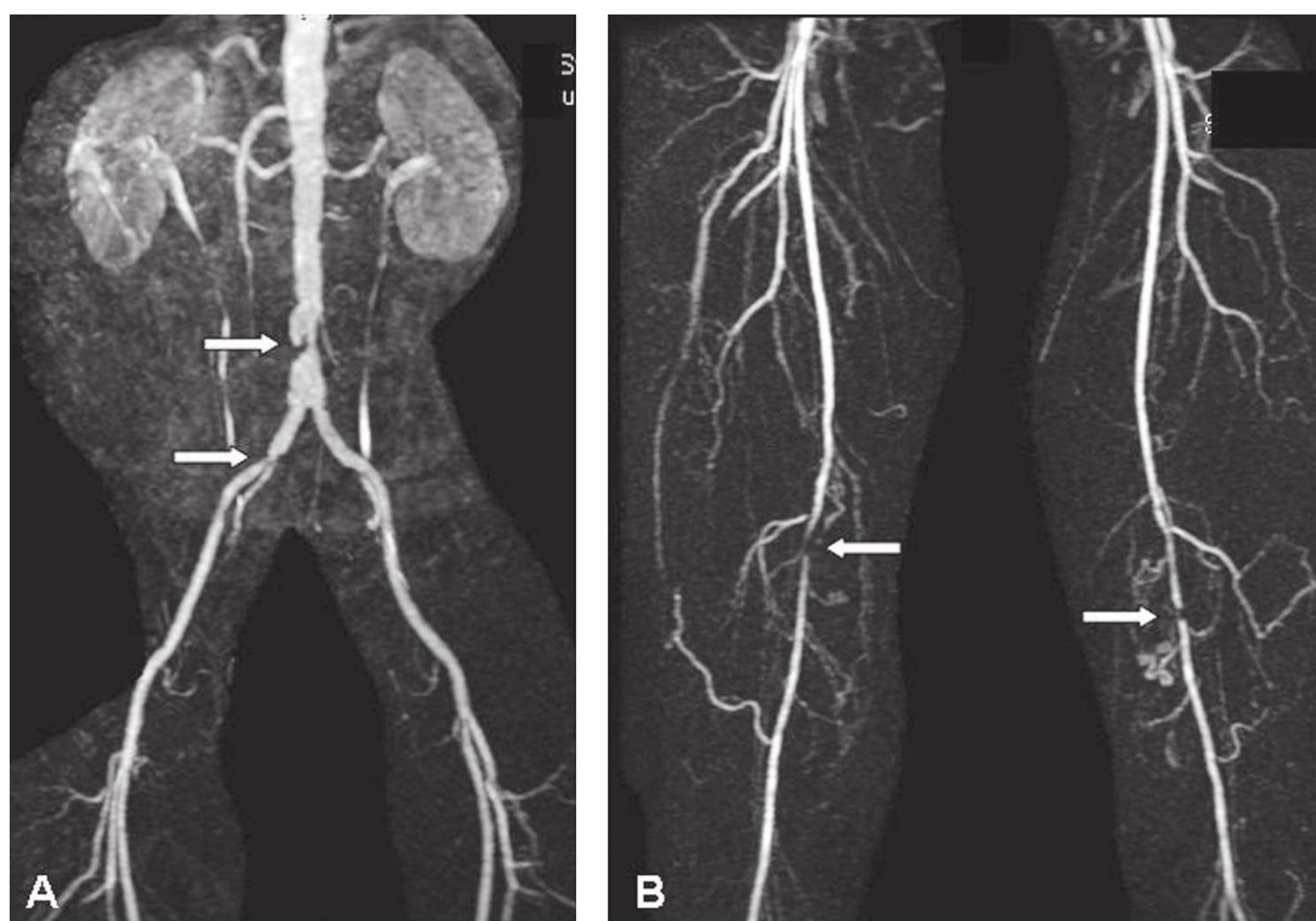


FIGURE 47-1

Magnetic resonance angiography of a patient with intermittent claudication, showing stenoses of the distal abdominal aorta and right iliac common iliac artery (A) and stenoses of the right

and left superficial femoral arteries (B). (Courtesy of Dr. Edwin Graveriaux, with permission.)

with the most severe PAD. Measurement of ABI is useful for detecting PAD and identifying persons at risk for future atherothrombotic events. The likelihood of symptomatic progression of PAD is lower than the chance of succumbing to CAD. Approximately 75–80% of nondiabetic patients who present with mild to moderate claudication remain symptomatically stable. Deterioration is likely to occur in the remainder, with approximately 1–2% of the group ultimately developing critical limb ischemia each year. Approximately 25–30% of patients with critical limb ischemia undergo amputation within 1 year. The prognosis is worse in patients who continue to smoke cigarettes or have diabetes mellitus.

TREATMENT Peripheral Artery Disease

Patients with PAD should receive therapies to reduce the risk of associated cardiovascular events, such as myocardial infarction and death, and to improve limb symptoms, prevent progression to critical limb ischemia, and preserve limb viability. Risk factor modification and antiplatelet therapy should be initiated to improve cardiovascular outcomes. The importance of discontinuing cigarette smoking cannot be overemphasized. The physician must assume a major role in this lifestyle modification. Counseling and adjunctive drug therapy with the nicotine patch, bupropion, or varenicline increase smoking cessation rates and reduce recidivism. It is important to control blood pressure in hypertensive patients. Angiotensin-converting enzyme inhibitors may reduce the risk of cardiovascular events in patients with symptomatic PAD. β -Adrenergic blockers do not worsen claudication and may be used to treat hypertension, especially in patients with coexistent CAD. Treatment of hypercholesterolemia with statins is advocated to reduce the risk of myocardial infarction, stroke, and death. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommends high intensity statin treatment in patients with atherosclerotic disorders, including peripheral artery disease. Platelet inhibitors, including aspirin and clopidogrel, reduce the risk of adverse cardiovascular events in patients with atherosclerosis and are recommended for patients with symptomatic PAD, including those with intermittent claudication or critical limb ischemia or prior lower extremity revascularization. Dual antiplatelet therapy with both aspirin and clopidogrel is not more effective than aspirin alone in reducing cardiovascular morbidity and mortality rates in patients with PAD. The anticoagulant warfarin is as effective as antiplatelet therapy in preventing adverse cardiovascular events but causes more major bleeding; therefore, it is not indicated to improve outcomes in patients with chronic PAD.

Therapies for intermittent claudication and critical limb ischemia include supportive measures, medications, non-operative interventions, and surgery. Supportive measures

include meticulous care of the feet, which should be kept clean and protected against excessive drying with moisturizing creams. Well-fitting and protective shoes are advised to reduce trauma. Elastic support hose should be avoided, as it reduces blood flow to the skin. In patients with critical limb ischemia, shock blocks under the head of the bed together with a canopy over the feet may improve perfusion pressure and ameliorate some of the rest pain.

Patients with claudication should be encouraged to exercise regularly and at progressively more strenuous levels. Supervised exercise training programs for 30- to 45-min sessions, three to five times per week for at least 12 weeks, prolong walking distance. Patients also should be advised to walk until nearly maximum claudication discomfort occurs and then rest until the symptoms resolve before resuming ambulation. The beneficial effect of supervised exercise training on walking performance in patients with claudication often is similar to or greater than that realized after a revascularization procedure. Pharmacologic treatment of PAD has not been as successful as the medical treatment of CAD (**Chap. 39**). In particular, vasodilators as a class have not proved to be beneficial. During exercise, peripheral vasodilation occurs distal to sites of significant arterial stenoses. As a result, perfusion pressure falls, often to levels lower than that generated in the interstitial tissue by the exercising muscle. Drugs such as α -adrenergic blocking agents, calcium channel antagonists, and other vasodilators have not been shown to be effective in patients with PAD.

Cilostazol, a phosphodiesterase inhibitor with vasodilator and antiplatelet properties, increases claudication distance by 40–60% and improves measures of quality of life. The mechanism of action accounting for its beneficial effects is not known. Pentoxifylline, a substituted xanthine derivative, increases blood flow to the microcirculation and enhances tissue oxygenation. Although several placebo-controlled studies have found that pentoxifylline increases the duration of exercise in patients with claudication, its efficacy has not been confirmed in all clinical trials. Statins and angiotensin-converting enzyme inhibitors appear promising for treatment of intermittent claudication in initial clinical trials, but more studies are needed to confirm the efficacy of each class of drugs. There is no definitive medical therapy for critical limb ischemia, although several studies have suggested that long-term parenteral administration of vasodilator prostaglandins decreases pain and facilitates healing of ulcers. Enthusiasm for therapy with angiogenic growth factors abated when clinical trials of intramuscular gene transfer of DNA encoding vascular endothelial growth factor, fibroblast growth factor, hepatocyte growth factor, or hypoxia-inducible factor 1 α failed to demonstrate improvement in symptoms or outcomes in patients with intermittent claudication or critical limb ischemia. Clinical trials assessing the ability of bone marrow-derived vascular progenitor cells to promote angiogenesis and preserve limb viability in patients with critical limb ischemia are ongoing.

REVASCULARIZATION Revascularization procedures, including catheter-based and surgical interventions, are usually indicated for patients with disabling, progressive, or severe symptoms of intermittent claudication despite medical therapy and for those with critical limb ischemia. MRA, CTA, or conventional angiography should be performed to assess vascular anatomy in patients who are being considered for revascularization. Nonoperative interventions include percutaneous transluminal angiography (PTA) and stent placement (**Chap. 42**). PTA and stenting of the iliac artery are associated with higher success rates than are PTA and stenting of the femoral and popliteal arteries. Approximately 90–95% of iliac PTAs are initially successful, and the 3-year patency rate is >75%. Patency rates may be higher if a stent is placed in the iliac artery. The initial success rates for femoral-popliteal PTA and stenting are approximately 80%, with 60% 3-year patency rates. Patency rates are influenced by the severity of pretreatment stenoses; the prognosis of occlusive lesions is worse than that of non-occlusive stenotic lesions. The role of drug-eluting stents and drug-coated balloons in PAD is under investigation.

Several operative procedures are available for treating patients with aortoiliac and femoral-popliteal artery disease. The preferred operative procedure depends on the location and extent of the obstruction(s) and the general medical condition of the patient. Operative procedures for aortoiliac disease include aortobifemoral bypass, axillofemoral bypass, femoro-femoral bypass, and aortoiliac endarterectomy. The most frequently used procedure is the aortobifemoral bypass using knitted Dacron grafts. Immediate graft patency approaches 99%, and 5- and 10-year graft patency rates in survivors are >90% and 80%, respectively. Operative complications include myocardial infarction and stroke, infection of the graft, peripheral embolization, and sexual dysfunction from interruption of autonomic nerves in the pelvis. The operative mortality rate ranges from 1–3%, mostly due to ischemic heart disease.

Operative therapy for femoral-popliteal artery disease includes in situ and reverse autogenous saphenous vein bypass grafts, placement of polytetrafluoroethylene (PTFE) or other synthetic grafts, and thromboendarterectomy. The operative mortality rate ranges from 1–3%. The long-term patency rate depends on the type of graft used, the location of the distal anastomosis, and the patency of runoff vessels beyond the anastomosis. Patency rates of femoral-popliteal saphenous vein bypass grafts approach 90% at 1 year and 70–80% at 5 years. Five-year patency rates of infrapopliteal saphenous vein bypass grafts are 60–70%. In contrast, 5-year patency rates of infrapopliteal PTFE grafts are <30%.

Preoperative cardiac risk assessment may identify individuals who are especially likely to experience an adverse cardiac event during the perioperative period. Patients with angina, prior myocardial infarction, ventricular ectopy, heart failure, or diabetes are among those at increased risk. Stress testing with treadmill exercise (if feasible), radionuclide myocardial perfusion imaging, or echocardiography permits further stratification of risk in these patients (**Chap. 42**). Patients with abnormal test results require close supervision

and adjunctive management with anti-ischemic medications. β -Adrenergic blockers and statins reduce the risk of postoperative cardiovascular complications. Coronary angiography and coronary artery revascularization compared with optimal medical therapy do not improve outcomes in most patients undergoing peripheral vascular surgery, but cardiac catheterization should be considered in patients with unstable angina and angina refractory to medical therapy as well as those suspected of having left main or three-vessel CAD.

FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia is a hyperplastic disorder that affects medium-size and small arteries. It occurs predominantly in females and usually involves the renal and carotid arteries but can affect extremity vessels such as the iliac and subclavian arteries. The histologic classification includes intimal fibroplasia (also classified as focal), medial dysplasia (multifocal), and adventitial hyperplasia. Medial dysplasia is subdivided into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia. Medial fibroplasia is the most common type and is characterized by alternating areas of thinned media and fibromuscular ridges. The internal elastic lamina usually is preserved. The iliac arteries are the limb arteries most likely to be affected by fibromuscular dysplasia. It is identified angiographically by a “string of beads” appearance caused by thickened fibromuscular ridges contiguous with thin, less-involved portions of the arterial wall, which is typical of medial fibroplasia. When limb vessels are involved, clinical manifestations are similar to those for atherosclerosis, including claudication and rest pain. PTA and surgical reconstruction have been beneficial in patients with debilitating symptoms or threatened limbs.

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (Buerger’s disease) is an inflammatory occlusive vascular disorder involving small and medium-size arteries and veins in the distal upper and lower extremities. Cerebral, visceral, and coronary vessels may be affected rarely. This disorder develops most frequently in men <40 years of age. The prevalence is higher in Asians and individuals of Eastern European descent. Although the cause of thromboangiitis obliterans is not known, there is a definite relationship to cigarette smoking in patients with this disorder.

In the initial stages of thromboangiitis obliterans, polymorphonuclear leukocytes infiltrate the walls of the small and medium-size arteries and veins. The internal elastic lamina is preserved, and a cellular, inflammatory thrombus develops in the vascular lumen. As the disease progresses, mononuclear cells, fibroblasts, and giant cells replace the neutrophils. Later stages are

characterized by perivascular fibrosis, organized thrombus, and recanalization.

The clinical features of thromboangiitis obliterans often include a triad of claudication of the affected extremity, Raynaud's phenomenon, and migratory superficial vein thrombophlebitis. Claudication usually is confined to the calves and feet or the forearms and hands because this disorder primarily affects distal vessels. In the presence of severe digital ischemia, trophic nail changes, painful ulcerations, and gangrene may develop at the tips of the fingers or toes. The physical examination shows normal brachial and popliteal pulses but reduced or absent radial, ulnar, and/or tibial pulses. MRA, CTA, and conventional arteriography are helpful in making the diagnosis. Smooth, tapering segmental lesions in the distal vessels are characteristic, as are collateral vessels at sites of vascular occlusion. Proximal atherosclerotic disease is usually absent. The diagnosis can be confirmed by excisional biopsy and pathologic examination of an involved vessel.

There is no specific treatment except abstention from tobacco. The prognosis is worse in individuals who continue to smoke, but results are discouraging even in those who stop smoking. Arterial bypass of the larger vessels may be used in selected instances, as well as local debridement, depending on the symptoms and severity of ischemia. Antibiotics may be useful; anticoagulants and glucocorticoids are not helpful. If these measures fail, amputation may be required.

VASCULITIS

Other vasculitides may affect the arteries that supply the upper and lower extremities.

ACUTE LIMB ISCHEMIA

Acute limb ischemia occurs when arterial occlusion results in the sudden cessation of blood flow to an extremity. The severity of ischemia and the viability of the extremity depend on the location and extent of the occlusion and the presence and subsequent development of collateral blood vessels. Principal causes of acute arterial occlusion include embolism, thrombus in situ, arterial dissection, and trauma.

The most common sources of arterial emboli are the heart, aorta, and large arteries. Cardiac disorders that cause thromboembolism include atrial fibrillation, both chronic and paroxysmal; acute myocardial infarction; ventricular aneurysm; cardiomyopathy; infectious and marantic endocarditis; thrombi associated with prosthetic heart valves; and atrial myxoma. Emboli to the distal vessels may also originate from proximal sites of atherosclerosis and aneurysms of the aorta and large vessels. Less frequently, an arterial occlusion results

paradoxically from a venous thrombus that has entered the systemic circulation via a patent foramen ovale or another septal defect. Arterial emboli tend to lodge at vessel bifurcations because the vessel caliber decreases at those sites; in the lower extremities, emboli lodge most frequently in the femoral artery, followed by the iliac artery, aorta, and popliteal and tibioperoneal arteries.

Acute arterial thrombosis in situ occurs most frequently in atherosclerotic vessels at the site of an atherosclerotic plaque or aneurysm and in arterial bypass grafts. Trauma to an artery may disrupt continuity of blood flow and cause acute limb ischemia via formation of an acute arterial thrombus or by disruption of an artery's integrity and extravasation of blood. Arterial occlusion may complicate arterial punctures and placement of catheters; it also may result from arterial dissection if the intimal flap obstructs the artery. Less common causes include thoracic outlet compression syndrome, which causes subclavian artery occlusion, and entrapment of the popliteal artery by abnormal placement of the medial head of the gastrocnemius muscle. Polycythemia and hypercoagulable disorders are also associated with acute arterial thrombosis.

CLINICAL FEATURES

The symptoms of an acute arterial occlusion depend on the location, duration, and severity of the obstruction. Often, severe pain, paresthesia, numbness, and coldness develop in the involved extremity within 1 hour. Paralysis may occur with severe and persistent ischemia. Physical findings include loss of pulses distal to the occlusion, cyanosis or pallor, mottling, decreased skin temperature, muscle stiffening, loss of sensation, weakness, and/or absent deep tendon reflexes. If acute arterial occlusion occurs in the presence of an adequate collateral circulation, as is often the case in acute graft occlusion, the symptoms and findings may be less impressive. In this situation, the patient complains about an abrupt decrease in the distance walked before claudication occurs or of modest pain and paresthesia. Pallor and coolness are evident, but sensory and motor functions generally are preserved. The diagnosis of acute limb ischemia is usually apparent from the clinical presentation. In most circumstances, MRA, CTA, or catheter-based arteriography is used to confirm the diagnosis and demonstrate the location and extent of arterial occlusion.

TREATMENT Acute Limb Ischemia

Once the diagnosis is made, the patient should be anticoagulated with intravenous heparin to prevent propagation of the clot. In cases of severe ischemia of recent onset, particularly

when limb viability is jeopardized, immediate intervention to ensure reperfusion is indicated. Catheter-directed thrombolysis/thrombectomy, surgical thromboembolectomy, and arterial bypass procedures are used to restore blood flow to the ischemic extremity promptly, particularly when a large proximal vessel is occluded.

Intraarterial thrombolytic therapy with recombinant tissue plasminogen activator, reteplase, or tenecteplase is most effective when acute arterial occlusion is recent (<2 weeks) and caused by a thrombus in an atherosclerotic vessel, arterial bypass graft, or occluded stent. Thrombolytic therapy is also indicated when the patient's overall condition contraindicates surgical intervention or when smaller distal vessels are occluded, thus preventing surgical access. Meticulous observation for hemorrhagic complications is required during intraarterial thrombolytic therapy. Another endovascular approach to thrombus removal is percutaneous mechanical thrombectomy using devices that employ hydrodynamic forces or rotating baskets to fragment and remove the clot. These treatments may be used alone but usually are used in conjunction with pharmacologic thrombolysis. Surgical revascularization is preferred when restoration of blood flow must occur within 24 h to prevent limb loss or when symptoms of occlusion have been present for more than 2 weeks. Amputation is performed when the limb is not viable, as characterized by loss of sensation, paralysis, and the absence of Doppler-detected blood flow in both arteries and veins.

If the limb is not in jeopardy, a more conservative approach that includes observation and administration of anticoagulants may be taken. Anticoagulation prevents recurrent embolism and reduces the likelihood of thrombus propagation; it can be initiated with intravenous heparin and followed by oral warfarin. Recommended doses are the same as those used for deep vein thrombosis (**Chap. 45**). Emboli resulting from infective endocarditis, the presence of prosthetic heart valves, or atrial myxoma often require surgical intervention to remove the cause.

ATHEROEMBOLISM

Atheroembolism is another cause of limb ischemia. In this condition, multiple small deposits of fibrin, platelets, and cholesterol debris embolize from proximal atherosclerotic lesions or aneurysmal sites. Large protruding aortic atheromas are a source of emboli that may lead to limb ischemia, as well as stroke and renal insufficiency. Atheroembolism may occur after intraarterial procedures. Since atheroemboli to limbs tend to lodge in the small vessels of the muscle and skin and may not occlude the large vessels, distal pulses usually remain palpable. Patients complain of acute pain and tenderness at the site of embolization. Digital vascular occlusion may result in ischemia and the “blue toe” syndrome; digital necrosis and gangrene may develop (**Fig. 47-2**). Localized areas of tenderness, pallor, and livedo reticularis (see below)



FIGURE 47-2

Atheroembolism causing cyanotic discoloration and impending necrosis of the toes (“blue toe” syndrome).

occur at sites of emboli. Skin or muscle biopsy may demonstrate cholesterol crystals.

Ischemia resulting from atheroemboli is notoriously difficult to treat. Usually neither surgical revascularization procedures nor thrombolytic therapy is helpful because of the multiplicity, composition, and distal location of the emboli. There is limited evidence that antithrombotic therapy with platelet inhibitors or anticoagulants prevents atheroembolism. Statins may stabilize plaque and potentially reduce the risk of atheroembolism. Surgical intervention to remove or bypass the atherosclerotic vessel or aneurysm that causes the recurrent atheroemboli may be necessary.

THORACIC OUTLET COMPRESSION SYNDROME

This is a symptom complex resulting from compression of the neurovascular bundle (artery, vein, or nerves) at the thoracic outlet as it courses through the neck and shoulder. Cervical ribs, abnormalities of the scalenus anticus muscle, proximity of the clavicle to the first rib, or abnormal insertion of the pectoralis minor muscle may compress the subclavian artery, subclavian vein, and brachial plexus as these structures pass from the thorax to the arm. Depending on the structures affected, thoracic outlet compression syndrome is divided into arterial, venous, and neurogenic forms. Patients with neurogenic thoracic outlet compression may develop shoulder and arm pain, weakness, and paresthesias. Patients with arterial compression may experience claudication, Raynaud's phenomenon, and even ischemic tissue loss and gangrene. Venous compression may cause thrombosis of the subclavian and axillary veins; this is often associated with effort and is referred to as Paget-Schroetter syndrome.

APPROACH TO THE PATIENT

Thoracic Outlet Compression Syndrome

Examination of a patient with arterial thoracic outlet compression syndrome is often normal unless provocative maneuvers are performed. Occasionally, distal pulses are decreased or absent and digital cyanosis and ischemia may be evident.

Several maneuvers that support the diagnosis of arterial thoracic outlet compression syndrome may be used to precipitate symptoms, cause a subclavian artery bruit, and diminish arm pulses. These maneuvers include the abduction and external rotation test, in which the affected arm is abducted by 90° and the shoulder is externally rotated; the scalene maneuver (extension of the neck and rotation of the head to the side of the symptoms); the costoclavicular maneuver (posterior rotation of shoulders); and the hyperabduction maneuver (raising the arm 180°). A chest x-ray will indicate the presence of cervical ribs. Duplex ultrasonography, MRA, and contrast angiography can be performed during provocative maneuvers to demonstrate thoracic outlet compression of the subclavian artery. Neurophysiologic tests such as the electromyogram, nerve conduction studies, and somatosensory evoked potentials may be abnormal if the brachial plexus is involved, but the diagnosis of neurogenic thoracic outlet syndrome is not necessarily excluded if these tests are normal owing to their low sensitivity.

Most patients can be managed conservatively. They should be advised to avoid the positions that cause symptoms. Many patients benefit from shoulder girdle exercises. Surgical procedures such as removal of the first rib and resection of the scalenus anticus muscle are necessary occasionally for relief of symptoms or treatment of ischemia.

POPLITEAL ARTERY ENTRAPMENT

Popliteal artery entrapment typically affects young athletic men and women when the gastrocnemius or popliteus muscle compresses the popliteal artery and causes intermittent claudication. Thrombosis, embolism, or popliteal artery aneurysm may occur. The pulse examination may be normal unless provocative maneuvers such as ankle dorsiflexion and plantar flexion are performed. The diagnosis is confirmed by duplex ultrasound, CTA, MRA, or conventional angiography. Treatment involves surgical release of the popliteal artery or vascular reconstruction.

POPLITEAL ARTERY ANEURYSM

Popliteal artery aneurysms are the most common peripheral artery aneurysms. Approximately 50% are bilateral. Patients with popliteal artery aneurysms often have aneurysms of other arteries, especially the aorta. The most common clinical presentation is limb

ischemia secondary to thrombosis or embolism. Rupture occurs less frequently. Other complications include compression of the adjacent popliteal vein or peroneal nerve. Popliteal artery aneurysm can be detected by palpation and confirmed by duplex ultrasonography. Repair is indicated for symptomatic aneurysms or when the diameter exceeds 2–3 cm, owing to the risk of thrombosis, embolism, or rupture.

ARTERIOVENOUS FISTULA

Abnormal communications between an artery and a vein, bypassing the capillary bed, may be congenital or acquired. Congenital arteriovenous fistulas are a result of persistent embryonic vessels that fail to differentiate into arteries and veins; they may be associated with birthmarks, can be located in almost any organ of the body, and frequently occur in the extremities. Acquired arteriovenous fistulas either are created to provide vascular access for hemodialysis or occur as a result of a penetrating injury such as a gunshot or knife wound or as complications of arterial catheterization or surgical dissection. An uncommon cause of arteriovenous fistula is rupture of an arterial aneurysm into a vein.

The clinical features depend on the location and size of the fistula. Frequently, a pulsatile mass is palpable, and a thrill and a bruit lasting throughout systole and diastole are present over the fistula. With long-standing fistulas, clinical manifestations of chronic venous insufficiency, including peripheral edema; large, tortuous varicose veins; and stasis pigmentation become apparent because of the high venous pressure. Evidence of ischemia may occur in the distal portion of the extremity. Skin temperature is higher over the arteriovenous fistula. Large arteriovenous fistulas may result in an increased cardiac output with consequent cardiomegaly and high-output heart failure (**Chap. 19**).

The diagnosis is often evident from the physical examination. Compression of a large arteriovenous fistula may cause reflex slowing of the heart rate (Nicoladoni-Branham sign). Duplex ultrasonography may detect an arteriovenous fistula, especially one that affects the femoral artery and vein at the site of catheter access. CTA and conventional angiography can confirm the diagnosis and are useful in demonstrating the site and size of the arteriovenous fistula.

Management of arteriovenous fistulas may involve surgery, radiotherapy, or embolization. Congenital arteriovenous fistulas are often difficult to treat because the communications may be numerous and extensive, and new communications frequently develop after ligation of the most obvious ones. Many of these lesions are best treated conservatively using elastic support hose to reduce the consequences of venous hypertension. Occasionally, embolization with autologous material,

such as fat or muscle, or with hemostatic agents, such as gelatin sponges or silicon spheres, is used to obliterate the fistula. Acquired arteriovenous fistulas are usually amenable to surgical treatment that involves division or excision of the fistula. Occasionally, autogenous or synthetic grafting is necessary to reestablish continuity of the artery and vein.

RAYNAUD'S PHENOMENON

Raynaud's phenomenon is characterized by episodic digital ischemia, manifested clinically by the sequential development of digital blanching, cyanosis, and rubor of the fingers or toes after cold exposure and subsequent rewarming. Emotional stress may also precipitate Raynaud's phenomenon. The color changes are usually well demarcated and are confined to the fingers or toes. Typically, one or more digits will appear white when the patient is exposed to a cold environment or touches a cold object (**Fig. 47-3A**). The blanching, or pallor, represents the ischemic phase of the phenomenon and

results from vasospasm of digital arteries. During the ischemic phase, capillaries and venules dilate, and cyanosis results from the deoxygenated blood that is present in these vessels. A sensation of cold or numbness or paresthesia of the digits often accompanies the phases of pallor and cyanosis.

With rewarming, the digital vasospasm resolves, and blood flow into the dilated arterioles and capillaries increases dramatically. This "reactive hyperemia" imparts a bright red color to the digits. In addition to rubor and warmth, patients often experience a throbbing, painful sensation during the hyperemic phase. Although the triphasic color response is typical of Raynaud's phenomenon, some patients may develop only pallor and cyanosis; others may experience only cyanosis.

Raynaud's phenomenon is broadly separated into two categories: idiopathic, termed primary Raynaud's phenomenon, and secondary Raynaud's phenomenon, which is associated with other disease states or known causes of vasospasm (**Table 47-1**).



FIGURE 47-3

Vascular diseases associated with temperature: (A) Raynaud's phenomenon; (B) acrocyanosis; (C) livedo reticularis; (D) perniosis;

(E) erythromelalgia; and (F) frostbite.

TABLE 47-1

CLASSIFICATION OF RAYNAUD’S PHENOMENON
Primary or idiopathic Raynaud’s phenomenon
Secondary Raynaud’s phenomenon
Collagen vascular diseases: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis, mixed connective tissue disease, Sjögren’s syndrome
Arterial occlusive diseases: atherosclerosis of the extremities, thromboangiitis obliterans, acute arterial occlusion, thoracic outlet syndrome
Pulmonary hypertension
Neurologic disorders: intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome, complex regional pain syndrome
Blood dyscrasias: cold agglutinins, cryoglobulinemia, cryofibrinogenemia, myeloproliferative disorders, lymphoplasmacytic lymphoma
Trauma: vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing
Drugs and toxins: ergot derivatives, methysergide, β -adrenergic receptor blockers, bleomycin, vinblastine, cisplatin, gemcitabine, vinyl chloride

Primary Raynaud’s phenomenon

This appellation is applied when the secondary causes of Raynaud’s phenomenon have been excluded. Over 50% of patients with Raynaud’s phenomenon have the primary form. Women are affected about five times more often than men, and the age of presentation is usually between 20 and 40 years. The fingers are involved more frequently than the toes. Initial episodes may involve only one or two fingertips, but subsequent attacks may involve the entire finger and may include all the fingers. The toes are affected in 40% of patients. Although vasospasm of the toes usually occurs in patients with symptoms in the fingers, it may happen alone. Rarely, the earlobes, the tip of the nose, and the penis are involved. Raynaud’s phenomenon occurs frequently in patients who also have migraine headaches or variant angina. These associations suggest that there may be a common predisposing cause for the vasospasm. Results of physical examination are often entirely normal; the radial, ulnar, and pedal pulses are normal. The fingers and toes may be cool between attacks and may perspire excessively. Thickening and tightening of the digital subcutaneous tissue (sclerodactyly) develop in 10% of patients. Angiography of the digits for diagnostic purposes is not indicated.

In general, patients with primary Raynaud’s disease have milder clinical manifestations. Fewer than 1% of these patients lose a part of a digit. After the diagnosis is made, the disease improves spontaneously

in approximately 15% of patients and progresses in about 30%.

Secondary causes of Raynaud’s phenomenon

Raynaud’s phenomenon occurs in 80–90% of patients with systemic sclerosis (scleroderma) and is the presenting symptom in 30%. It may be the only symptom of scleroderma for many years. Abnormalities of the digital vessels may contribute to the development of Raynaud’s phenomenon in this disorder. Ischemic fingertip ulcers may develop and progress to gangrene and autoamputation. About 20% of patients with systemic lupus erythematosus (SLE) have Raynaud’s phenomenon. Occasionally, persistent digital ischemia develops and may result in ulcers or gangrene. In most severe cases, the small vessels are occluded by a proliferative endarteritis. Raynaud’s phenomenon occurs in about 30% of patients with dermatomyositis or polymyositis. It frequently develops in patients with rheumatoid arthritis and may be related to the intimal proliferation that occurs in the digital arteries.

Atherosclerosis of the extremities is a common cause of Raynaud’s phenomenon in men >50 years. Thromboangiitis obliterans is an uncommon cause of Raynaud’s phenomenon but should be considered in young men, particularly those who are cigarette smokers. The development of cold-induced pallor in these disorders may be confined to one or two digits of the involved extremity. Occasionally, Raynaud’s phenomenon may follow acute occlusion of large and medium-size arteries by a thrombus or embolus. Embolization of atheroembolic debris may cause digital ischemia. The latter situation often involves one or two digits and should not be confused with Raynaud’s phenomenon. In patients with thoracic outlet compression syndrome, Raynaud’s phenomenon may result from diminished intravascular pressure, stimulation of sympathetic fibers in the brachial plexus, or a combination of both. Raynaud’s phenomenon occurs in patients with primary pulmonary hypertension (**Chap. 49**); this is more than coincidental and may reflect a neurohumoral abnormality that affects both the pulmonary and digital circulations.

A variety of blood dyscrasias may be associated with Raynaud’s phenomenon. Cold-induced precipitation of plasma proteins, hyperviscosity, and aggregation of red cells and platelets may occur in patients with cold agglutinins, cryoglobulinemia, or cryofibrinogenemia. Hyperviscosity syndromes that accompany myeloproliferative disorders and lymphoplasmacytic lymphoma (Waldenström’s macroglobulinemia) should also be considered in the initial evaluation of patients with Raynaud’s phenomenon.

Raynaud's phenomenon occurs often in patients whose vocations require the use of vibrating hand tools, such as chain saws or jackhammers. The frequency of Raynaud's phenomenon also seems to be increased in pianists and keyboard operators. Electric shock injury to the hands or frostbite may lead to the later development of Raynaud's phenomenon.

Several drugs have been causally implicated in Raynaud's phenomenon. They include ergot preparations, methysergide, β -adrenergic receptor antagonists, and the chemotherapeutic agents bleomycin, vinblastine, cisplatin, and gemcitabine.

TREATMENT Raynaud's Phenomenon

Most patients with Raynaud's phenomenon experience only mild and infrequent episodes. These patients need reassurance and should be instructed to dress warmly and avoid unnecessary cold exposure. In addition to gloves and mittens, patients should protect the trunk, head, and feet with warm clothing to prevent cold-induced reflex vasoconstriction. Tobacco use is contraindicated.

Drug treatment should be reserved for severe cases. Dihydropyridine calcium channel antagonists such as nifedipine, isradipine, felodipine, and amlodipine decrease the frequency and severity of Raynaud's phenomenon. Diltiazem may be considered but is less effective. The postsynaptic α_1 -adrenergic antagonist prazosin has been used with favorable responses; doxazosin and terazosin may also be effective. Phosphodiesterase type 5 inhibitors such as sildenafil and tadalafil may improve symptoms in patients with secondary Raynaud's phenomenon, as occurs with systemic sclerosis. Digital sympathectomy is helpful in some patients who are unresponsive to medical therapy.

ACROCYANOSIS

In this condition, there is arterial vasoconstriction and secondary dilation of the capillaries and venules with resulting persistent cyanosis of the hands and, less frequently, the feet. Cyanosis may be intensified by exposure to a cold environment. Acrocyanosis may be categorized as primary or secondary to an underlying condition. In primary acrocyanosis, women are affected much more frequently than men, and the age of onset is usually <30 years. Generally, patients are asymptomatic but seek medical attention because of the discoloration. The prognosis is favorable, and pain, ulcers, and gangrene do not occur. Examination reveals normal pulses, peripheral cyanosis, and moist palms (Fig. 47-3B). Trophic skin changes and ulcerations do not occur. The disorder can be distinguished from Raynaud's phenomenon because it is persistent and not episodic, the discoloration extends proximally from the

digits, and blanching does not occur. Ischemia secondary to arterial occlusive disease can usually be excluded by the presence of normal pulses. Central cyanosis and decreased arterial oxygen saturation are not present. Patients should be reassured and advised to dress warmly and avoid cold exposure. Pharmacologic intervention is not indicated.

Secondary acrocyanosis may result from hypoxemia, vasopressor medications, connective tissue diseases, atheroembolism, antiphospholipid antibodies, cold agglutinins, or cryoglobulins and is associated with anorexia nervosa and postural orthostatic tachycardia syndrome. Treatment should be directed at the underlying disorder.

LIVEDO RETICULARIS

In this condition, localized areas of the extremities develop a mottled or rete (netlike) appearance of reddish to blue discoloration (Fig. 47-3C). The mottled appearance may be more prominent after cold exposure. There are primary and secondary forms of livedo reticularis. The primary, or idiopathic, form of this disorder may be benign or associated with ulcerations. The benign form occurs more frequently in women than in men, and the most common age of onset is the third decade. Patients with the benign form are usually asymptomatic and seek attention for cosmetic reasons. These patients should be reassured and advised to avoid cold environments. No drug treatment is indicated. Primary livedo reticularis with ulceration is also called *atrophie blanche en plaque*. The ulcers are painful and may take months to heal. Secondary livedo reticularis can occur with atheroembolism (see above), SLE and other vasculitides, anticardiolipin antibodies, hyperviscosity, cryoglobulinemia, and Sneddon's syndrome (ischemic stroke and livedo reticularis). Rarely, skin ulcerations develop.

PERNIO (CHILBLAINS)

Pernio is a vasculitic disorder associated with exposure to cold; acute forms have been described. Raised erythematous lesions develop on the lower part of the legs and feet in cold weather (Fig. 47-3D). They are associated with pruritus and a burning sensation, and they may blister and ulcerate. Pathologic examination demonstrates angitis characterized by intimal proliferation and perivascular infiltration of mononuclear and polymorphonuclear leukocytes. Giant cells may be present in the subcutaneous tissue. Patients should avoid exposure to cold, and ulcers should be kept clean and protected with sterile dressings. Sympatholytic drugs and dihydropyridine calcium channel antagonists may be effective in some patients.

ERYTHROMELALGIA

This disorder is characterized by burning pain and erythema of the extremities (Fig. 47-3E). The feet are involved more frequently than the hands, and males are affected more frequently than females. Erythromelalgia may occur at any age but is most common in middle age. It may be primary (also termed erythermalgia) or secondary. Mutations in the SCN9A gene, which encodes the Nav1.7 voltage-gated sodium channel expressed in sensory and sympathetic nerves, has been described in inherited forms of erythromelalgia. The most common causes of secondary erythromelalgia are myeloproliferative disorders such as polycythemia vera and essential thrombocytosis. Less common causes include drugs, such as calcium channel blockers, bromocriptine, and pergolide; neuropathies; connective tissue diseases such as SLE; and paraneoplastic syndromes. Patients complain of burning in the extremities that is precipitated by exposure to a warm environment and aggravated by a dependent position. The symptoms are relieved by exposing the affected area to cool air or water or by elevation. Erythromelalgia can be distinguished from ischemia secondary to peripheral arterial disorders because the peripheral pulses are present. There is no specific treatment; aspirin may produce relief in patients with erythromelalgia secondary to myeloproliferative disease. Treatment of associated disorders in secondary erythromelalgia may be helpful.

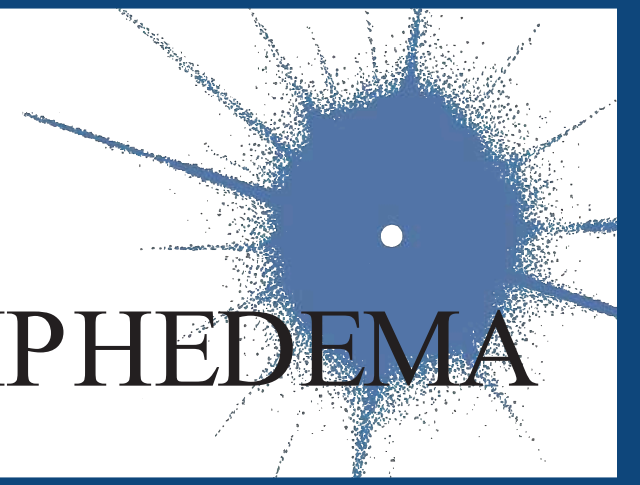
FROSTBITE

In this condition, tissue damage results from severe environmental cold exposure or from direct contact with a very cold object. Tissue injury results from both freezing and vasoconstriction. Frostbite usually affects the distal aspects of the extremities or exposed parts of the face, such as the ears, nose, chin, and cheeks. Superficial frostbite involves the skin and subcutaneous tissue. Patients experience pain or paresthesia, and the skin appears white and waxy. After rewarming, there is cyanosis and erythema, wheal-and-flare formation, edema, and superficial blisters. Deep frostbite involves muscle, nerves, and deeper blood vessels. It may result in edema of the hand or foot, vesicles and bullae, tissue necrosis, and gangrene (Fig. 47-3F).

Initial treatment is rewarming, performed in an environment where reexposure to freezing conditions will not occur. Rewarming is accomplished by immersion of the affected part in a water bath at temperatures of 40°–44°C (104°–111°F). Massage, application of ice water, and extreme heat are contraindicated. The injured area should be cleansed with soap or antiseptic, and sterile dressings should be applied. Analgesics are often required during rewarming. Antibiotics are used if there is evidence of infection. The efficacy of sympathetic blocking drugs is not established. After recovery, the affected extremity may exhibit increased sensitivity to cold.

CHAPTER 48

CHRONIC VENOUS DISEASE AND LYMPHEDEMA



Mark A. Creager ■ Joseph Loscalzo

CHRONIC VENOUS DISEASE

Chronic venous diseases range from telangiectasias and reticular veins, to varicose veins, to chronic venous insufficiency with edema, skin changes, and ulceration. This section of the chapter will focus on identification and treatment of varicose veins and chronic venous insufficiency, since these problems are encountered frequently by the internist. The estimated prevalence of varicose veins in the United States is approximately 15% in men and 30% in women. Chronic venous insufficiency with edema affects approximately 7.5% of men and 5% of women, and the prevalence increases with age ranging from 2% among those less than 50 years of age to 10% of those 70 years of age. Approximately 20% of patients with chronic venous insufficiency develop venous ulcers.

VENOUS ANATOMY

Veins in the extremities can be broadly classified as either superficial or deep. The superficial veins are located between the skin and deep fascia. In the legs, these include the great and small saphenous veins and their tributaries. The great saphenous vein is the longest vein in the body. It originates on the medial side of the foot and ascends anterior to the medial malleolus and then along the medial side of the calf and thigh, and drains into the common femoral vein. The small saphenous vein originates on the dorsolateral aspect of the foot, ascends posterior to the lateral malleolus and along the posterolateral aspect of the calf, and drains into the popliteal vein. The deep veins of the leg accompany the major arteries. There are usually paired peroneal, anterior tibial, and posterior tibial veins in the calf, which converge to form the popliteal vein. Soleal tributary veins drain into the posterior tibial or peroneal veins, and gastrocnemius tributary veins drain into the popliteal vein. The popliteal vein ascends in

the thigh as the femoral vein. The confluence of the femoral vein and deep femoral vein form the common femoral vein, which ascends in the pelvis as the external iliac and then common iliac vein, which converges with the contralateral common iliac vein at the inferior vena cava. Perforating veins connect the superficial and deep systems in the legs at multiple locations, normally allowing blood to flow from the superficial to deep veins. In the arms, the superficial veins include the basilic, cephalic, and median cubital veins and their tributaries. The basilic and cephalic veins course along the medial and lateral aspects of the arm, respectively, and these are connected via the median cubital vein in the antecubital fossa. The deep veins of the arms accompany the major arteries and include the radial, ulnar, brachial, axillary, and subclavian veins. The subclavian vein converges with the internal jugular vein to form the brachiocephalic vein, which joins the contralateral brachiocephalic vein to form the superior vena cava. Bicuspid valves are present throughout the venous system to direct the flow of venous blood centrally.

Pathophysiology of chronic venous disease

Varicose veins are dilated, bulging, tortuous superficial veins, measuring at least 3 mm in diameter. The smaller and less tortuous reticular veins are dilated intradermal veins, which appear blue-green, measure 1 to 3 mm in diameter, and do not protrude from the skin surface. Telangiectasias, or spider veins, are small, dilated veins, less than 1 mm in diameter, located near the skin surface, and form blue, purple, or red linear, branching, or spider-web patterns.

Varicose veins can be categorized as primary or secondary. Primary varicose veins originate in the superficial system and result from defective structure and function of the valves of the saphenous veins, intrinsic weakness of the vein wall, and high intraluminal pressure. Approximately one-half of these patients have a

family history of varicose veins. Other factors associated with primary varicose veins include aging, pregnancy, hormonal therapy, obesity, and prolonged standing. Secondary varicose veins result from venous hypertension, associated with deep venous insufficiency or deep venous obstruction, and incompetent perforating veins that cause enlargement of superficial veins. Arteriovenous fistulas also cause varicose veins in the affected limb.

Chronic venous insufficiency is a consequence of incompetent veins in which there is venous hypertension and extravasation of fluid and blood elements into the tissue of the limb. It may occur in patients with varicose veins but usually is caused by disease in the deep veins. It also is categorized as primary or secondary. Primary deep venous insufficiency is a consequence of an intrinsic structural or functional abnormality in the vein wall or venous valves leading to valvular reflux. Secondary deep venous insufficiency is caused by obstruction and/or valvular incompetence from previous deep vein thrombosis (**Chap. 45**). Deep venous insufficiency occurs following deep vein thrombosis, as the delicate valve leaflets become thickened and contracted and can no longer prevent retrograde flow of blood and the vein itself becomes rigid and thick walled. Although most veins recanalize after an episode of thrombosis, the large proximal veins may remain occluded. Secondary incompetence develops in distal valves because high pressures distend the vein and separate the leaflets. Other causes of secondary deep venous insufficiency include May-Turner syndrome, where the left iliac vein is occluded or stenosed by extrinsic compression from the overlapping right common iliac artery; arteriovenous fistulas resulting in increased venous pressure; congenital deep vein agenesis or hypoplasia; and venous malformations as may occur in Klippel-Trénaunay-Weber and Parkes-Weber syndromes.

Clinical presentation

Patients with venous varicosities are often asymptomatic but still concerned about the cosmetic appearance of their legs. Superficial venous thrombosis may be a recurring problem, and, rarely, a varicosity ruptures and bleeds. Symptoms in patients with varicose veins or venous insufficiency, when they occur, include a dull ache, throbbing or heaviness, or pressure sensation in the legs typically after prolonged standing; these symptoms usually are relieved with leg elevation. Additional symptoms may include cramping, burning, pruritus, leg swelling, and skin ulceration.

The legs are examined in both the supine and standing positions. Visual inspection and palpation of the legs in the standing position confirm the presence of varicose veins. The location and extent of the varicose veins should be noted. Edema, stasis dermatitis,

and skin ulceration near the ankle may be present if there is superficial venous insufficiency and venous hypertension. Findings of deep venous insufficiency include increased leg circumference, venous varicosities, edema, and skin changes. The edema, which is usually pitting, may be confined to the ankles, extend above the ankles to the knees, or involve the thighs in severe cases. Over time, the edema may become less pitting and more indurated. Dermatologic findings associated with venous stasis include hyperpigmentation, erythema, eczema, lipodermatosclerosis, atrophie blanche, and a phlebectasia corona. Lipodermatosclerosis is the combination of induration, hemosiderin deposition, and inflammation, and typically occurs in the lower part of the leg just above the ankle. Atrophie blanche is a white patch of scar tissue, often with focal telangiectasias and a hyperpigmented border; it usually develops near the medial malleolus. A phlebectasia corona is a fan-shaped pattern of intradermal veins near the ankle or on the foot. Skin ulceration may occur near the medial and lateral malleoli. A venous ulcer is often shallow and characterized by an irregular border, a base of granulation tissue, and the presence of exudate (**Fig. 48-1**).

Bedside maneuvers can be used to distinguish primary varicose veins from secondary varicose veins caused by deep venous insufficiency. With the contemporary use of venous ultrasound (see below), however, these maneuvers are employed infrequently. The Brodie-Trendelenburg test is used to determine whether varicose



FIGURE 48-1

Venous insufficiency with active venous ulcer near the medial malleolus. (Courtesy of Dr. Steven Dean, with permission.)

veins are secondary to deep venous insufficiency. As the patient is lying supine, the leg is elevated and the veins allowed to empty. Then, a tourniquet is placed on the proximal part of the thigh and the patient is asked to stand. Filling of the varicose veins within 30 s indicates that the varicose veins are caused by deep venous insufficiency and incompetent perforating veins. Primary varicose veins with superficial venous insufficiency are the likely diagnosis if venous refilling occurs promptly after tourniquet removal. The Perthes test assesses the possibility of deep venous obstruction. A tourniquet is placed on the midthigh after the patient has stood, and the varicose veins are filled. The patient is then instructed to walk for 5 min. A patent deep venous system and competent perforating veins enable the superficial veins below the tourniquet to collapse. Deep venous obstruction is likely to be present if the superficial veins distend further with walking.

Differential diagnosis

The duration of leg edema helps to distinguish chronic venous insufficiency from acute deep vein thrombosis. Lymphedema, as discussed later in this chapter, is often confused with chronic venous insufficiency, and both may occur together. Other disorders that cause leg swelling should be considered and excluded when evaluating a patient with presumed venous insufficiency. Bilateral leg swelling occurs in patients with congestive heart failure, hypoalbuminemia secondary to nephrotic syndrome or severe hepatic disease, myxedema caused by hypothyroidism or pretibial myxedema associated with Graves' disease, and with drugs such as dihydropyridine calcium channel blockers and thiazolidinediones. Unilateral causes of leg swelling also include ruptured leg muscles, hematomas secondary to trauma, and popliteal cysts. Cellulitis may cause erythema and swelling of the affected limb. Leg ulcers may be caused by severe peripheral artery disease and critical limb ischemia; neuropathies, particularly those associated with diabetes; and less commonly, skin cancer, vasculitis, or rarely as a complication of hydroxyurea. The location and characteristics of venous ulcers help to differentiate these from other causes.

Classification of chronic venous disease

The CEAP (clinical, etiologic, anatomic, pathophysiologic) classification schema incorporates the range of symptoms and signs of chronic venous disease to characterize its severity. It also broadly categorizes the etiology as congenital, primary, or secondary; identifies the affected veins as superficial, deep, or perforating; and characterizes the pathophysiology as reflux, obstruction, both, or neither (**Table 48-1**).

TABLE 48-1

CEAP (CLINICAL, ETIOLOGIC, ANATOMIC, PATHOPHYSIOLOGIC) CLASSIFICATION

Clinical Classification

C0 No visible or palpable signs of venous disease
C1 Telangiectasias, reticular veins
C2 Varicose veins
C3 Edema without skin changes
C4 Skin changes, including pigmentation, eczema, lipodermatosclerosis, and atrophie blanche
C5 Healed venous ulcer
C6 Active venous ulcer

Etiologic Classification

Ec Congenital
Ep Primary
Es Secondary (postthrombotic)
En No venous etiology identified

Anatomic Classification

As Superficial veins
Ap Perforator veins
Ad Deep veins
An No venous location identified

Pathophysiologic Classification

Pr Reflux
Po Obstruction
Pr,o Reflux and obstruction
Pn No venous pathophysiology identifiable

Source: BEklöf et al: J Vasc Surg 40:1248, 2004.

Diagnostic testing

The principal diagnostic test to evaluate patients with chronic venous disease is venous duplex ultrasonography. A venous duplex ultrasound examination uses a combination of B-mode imaging and spectral Doppler to detect the presence of venous obstruction and venous reflux in superficial and deep veins. Color-assisted Doppler ultrasound is useful to visualize venous flow patterns. Obstruction may be diagnosed by absence of flow, the presence of an echogenic thrombus within the vein, or failure of the vein to collapse when a compression maneuver is applied by the sonographer, the last implicating the presence of an intraluminal thrombus. Venous reflux is detected by prolonged reversal of venous flow direction during a Valsalva maneuver, particularly for the common femoral vein or saphenofemoral junction, or after compression and release of a cuff placed on the limb distal to the area being interrogated.

Some vascular laboratories use air or strain gauge plethysmography to assess the severity of venous reflux and complement findings from the venous ultrasound examination. Venous volume and venous refilling time are measured when the legs are placed in a dependent position and after calf exercise to quantify the severity of venous reflux and the efficiency of the calf muscle pump to affect venous return.

Magnetic resonance, computed tomographic, and conventional venography are rarely required to determine the cause and plan treatment for chronic venous insufficiency unless there is suspicion for pathology that might warrant intervention. These modalities are used to identify obstruction or stenosis of the inferior vena cava and iliofemoral veins, as may occur in patients with previous proximal deep vein thrombosis; occlusion of inferior vena cava filters; extrinsic compression from tumors; and May-Turner syndrome.

TREATMENT Chronic Venous Disease

SUPPORTIVE MEASURES Varicose veins usually are treated with conservative measures. Symptoms often decrease when the legs are elevated periodically, prolonged standing is avoided, and elastic support hose are worn. External compression with elastic stockings or stretch bandages provides a counterbalance to the hydrostatic pressure in the veins. Although compression garments may improve symptoms, they do not prevent progression of varicose veins. Graduated compression stockings with pressures of 20–30 mmHg are suitable for most patients with simple varicose veins, although pressures of 30–40 mmHg may be required for patients with manifestations of venous insufficiency such as edema and ulcers.

Patients with chronic venous insufficiency also should be advised to avoid prolonged standing or sitting; frequent leg elevation is helpful. Graded compression therapy consisting of stockings or multilayered compression bandages is the standard of care for advanced chronic venous insufficiency characterized by edema, skin changes, or venous ulcers defined as CEAP clinical class C3–C6. Graduated compression stockings of 30–40 mmHg are more effective than lesser grades for healing venous ulcers. The length of stocking depends on the distribution of edema. Calf-length stockings are tolerated better by most patients, particularly elderly patients; for patients with varicose veins or edema extending to the thigh, thigh-length stockings or panty hose should be considered. Overweight and obese patients should be advised to lose weight via caloric restriction and exercise.

In addition to a compression bandage or stocking, patients with venous ulcers also may be treated with low adherent absorbent dressings that take up exudates while maintaining a moist environment. Other types of dressings include hydrocolloid (an adhesive dressing comprised of polymers such as carboxymethylcellulose that absorbs exudates by forming a

gel), hydrogel (a nonabsorbent dressing comprising over 80% water or glycerin that moisturizes wounds), foam (an absorbent dressing made with polymers such as polyurethane), and alginate (an absorbent, biodegradable dressing that is derived from seaweed), but there is little evidence that these are more effective than low adherent absorbent dressings. The choice of specific dressing depends on the amount of drainage, presence of infection, and integrity of the skin surrounding the ulcer. Antibiotics are not indicated unless the ulcer is infected. The multilayered compression bandage or graduated compression garment is then put over the dressing.

MEDICAL THERAPIES There are no drugs approved by the U.S. Food and Drug Administration for the treatment of chronic venous insufficiency. Diuretics may reduce edema, but at the risk of volume depletion and compromise in renal function. Topical steroids may be used for a short period of time to treat inflammation associated with stasis dermatitis. Several herbal supplements, such as horse chestnut seed extract (aescin); flavonoids including diosmin, hesperidin, or the two combined as micronized purified flavonoid fraction; and French maritime pine bark extract, are touted to have venoconstrictive and anti-inflammatory properties. Although meta-analyses have suggested that aescin reduces edema, pruritus, and pain and that micronized purified flavonoid fraction in conjunction with compression therapy facilitates venous ulcer healing, there is insufficient evidence to recommend the general use of these substances in patients with chronic venous insufficiency.

INTERVENTIONAL AND SURGICAL THERAPIES Ablative procedures, including endovenous thermal ablation, sclerotherapy, and surgery, are used to treat varicose veins in selected patients who have persistent symptoms, great saphenous vein incompetence, and complications of venous insufficiency including dermatitis, edema, and ulcers. Ablative therapy may also be indicated for cosmetic reasons.

Endovenous thermal ablation procedures of the saphenous veins include endovenous laser therapy and radiofrequency ablation. To ablate the great saphenous vein, a catheter is placed percutaneously and advanced from the level of the knee to just below the saphenofemoral junction via ultrasound guidance. Thermal energy is then delivered as the catheter is pulled back. The heat injures the endothelium and media and promotes thrombosis and fibrosis, resulting in venous occlusion. Average 1- and 5-year occlusion rates exceed 90% following endovenous laser therapy and are slightly less after radiofrequency ablation. Deep vein thrombosis of the common femoral vein adjacent to the saphenofemoral junction is an uncommon but potential complication of endovenous thermal ablation. Other adverse effects of thermal ablation procedures include pain, paresthesias, bruising, hematoma, and hyperpigmentation.

Sclerotherapy involves the injection of a chemical into a vein to cause fibrosis and obstruction. Sclerosing agents approved by the U.S. Food and Drug Administration include

sodium tetradecyl sulfate, polidocanol, sodium morrhuate, and glycerin. The sclerosing agent is administered as a liquid or mixed with air or CO₂/O₂ to create a foam. It first is injected into the great saphenous vein or its affected tributaries, often with ultrasound guidance. Thereafter, smaller more distal veins and incompetent perforating veins are injected. Following completion of the procedure, elastic bandages are applied, or 30–40 mmHg compression stockings are worn for 1–2 weeks. Average 1- and 5-year occlusion rates are 81% and 74%, respectively, following sclerotherapy. Complications are uncommon and include deep vein thrombosis, hematomas, damage to adjacent saphenous or sural nerves, and infection. Anaphylaxis is a very rare but severe complication.

Surgical therapy usually involves ligation and stripping of the great and small saphenous veins. The procedure is performed under general anesthesia. Incisions are made at the groin and the upper calf. The great saphenous vein is ligated below the saphenofemoral junction, and a wire is inserted into the great saphenous vein and advanced distally. The proximal part of the great saphenous vein is secured to the wire and retrieved, i.e., stripped, via the calf incision. Stripping of the great saphenous vein below the knee and stripping of the small saphenous vein usually are not performed because of the respective risks of saphenous and sural nerve injury. Complications of great saphenous vein ligation and stripping include deep vein thrombosis, bleeding, hematoma, infection, and nerve injury. Recurrent varicose veins occur in up to 50% patients by 5 years, due to technical failures, deep venous insufficiency, and incompetent perforating veins.

Stab phlebectomy is another surgical treatment for varicose veins. A small incision is made alongside the varicose vein, and it is avulsed by means of a forceps or hook. The procedure may be performed in conjunction with saphenous vein ligation and stripping or thermal ablation. Subfascial endoscopic perforator surgery (SEPS) uses endoscopy to identify and occlude incompetent perforating veins. It also may be performed along with other ablative procedures.

Endovascular interventions, surgical bypass, and reconstruction of the valves of the deep veins are performed when feasible to treat patients with advanced chronic venous insufficiency who have not responded to other therapies. Catheter-based interventions, usually involving placement of endovenous stents, may be considered to treat some patients with chronic occlusions of the iliac veins. Technical success rates exceed 85% in most series, and long-term patency is achieved in approximately 75% of these patients. Iliocaval bypass, femoroiliac venous bypass, and femorofemoral crossover venous bypass are procedures used occasionally to treat iliofemoral vein occlusion; saphenopopliteal vein bypass can be used to treat chronic femoropopliteal vein obstruction. Long-term patency rates for venous bypass procedures generally exceed 60% and are associated with improvement in symptoms. Surgical reconstruction of the valves of the deep veins and valve transfer procedures are used to treat valvular incompetence. Valvuloplasty involves tightening the valve by commissural apposition. With valve transfer procedures,

a segment of vein with a competent valve, such as a brachial or axillary vein, or adjacent saphenous or deep femoral vein, is inserted as an interposition graft in the incompetent vein. Both valvuloplasty and vein transfer operations result in ulcer healing in the majority of patients, although success rates are somewhat better with valvuloplasty.

Lymphedema

Lymphedema is a chronic condition caused by impaired transport of lymph and characterized by swelling of one or more limbs and occasionally the trunk and genitalia. Fluid accumulates in interstitial tissues when there is an imbalance between lymph production and lymph absorption, a process governed in large part by Starling forces. Deficiency, reflux, or obstruction of lymph vessels perturbs the ability of the lymphatic system to reabsorb proteins that had been filtered by blood vessels, and the tissue osmotic load promotes interstitial accumulation of water. Persistent lymphedema leads to inflammatory and immune responses characterized by infiltration of mononuclear cells, fibroblasts, and adipocytes, leading to adipose and collagen deposition in the skin and subcutaneous tissues.

Lymphatic anatomy

Lymphatic capillaries are blind-ended tubes formed by a single layer of endothelial cells. The absent or widely fenestrated basement membrane of lymphatic capillaries allows access to interstitial proteins and particles. Lymphatic capillaries merge to form microlymphatic precollector vessels, which contain few smooth muscle cells. The precollector vessels drain into collecting lymphatic vessels, which comprise endothelial cells, a basement membrane, smooth muscle, and bileaflet valves. The collecting lymphatic vessels in turn merge to form larger lymphatic conduits. Analogous to venous anatomy, there are superficial and deep lymphatic vessels in the legs, which communicate at the popliteal and inguinal lymph nodes. Pelvic lymphatic vessels drain into the thoracic duct, which ascends from the abdomen to the thorax and connects with the left brachiocephalic vein. Lymph is propelled centrally by the phasic contractile activity of lymphatic smooth muscle and facilitated by the contractions of contiguous skeletal muscle. The presence of lymphatic valves ensures unidirectional flow.

Etiology

Lymphedema may be categorized as primary or secondary ([Table 48-2](#)). The prevalence of primary lymphedema is approximately 1.15 per 100,000 persons less than 20 years of age. Females are affected more

TABLE 48-2

CAUSES OF LYMPHEDEMA
Primary
Sporadic (no identified cause)
Genetic disorders
Milroy's disease
Meige's disease
Lymphedema-distichiasis syndrome
Cholestasis-lymphedema
Hypotrichosis-lymphedema-telangiectasia
Turner's syndrome
Klinefelter's syndrome
Trisomy 13, 18, or 21
Noonan's syndrome
Klippel-Trénaunay syndrome
Parkes-Weber syndrome
Hennekam's syndrome
Yellow nail syndrome
Intestinal lymphangiectasia syndrome
Lymphangiomyomatosis
Neurofibromatosis type 1
Secondary
Infection
Bacterial lymphangitis (Streptococcus pyogenes, Staphylococcus aureus)
Lymphogranuloma venereum (Chlamydia trachomatis)
Filariasis (Wucheria bancrofti, Brugia malayi, B. timori)
Tuberculosis
Neoplastic infiltration of lymph nodes
Lymphoma
Prostate
Others
Surgery or irradiation of axillary or inguinal lymph nodes for treatment of cancer
Iatrogenic
Lymphatic division (during peripheral bypass surgery, varicose vein surgery, or harvesting of saphenous veins)
Miscellaneous
Contact dermatitis
Rheumatoid arthritis
Pregnancy
Factitious

frequently than males. Primary lymphedema may be caused by agenesis, hypoplasia, hyperplasia, or obstruction of the lymphatic vessels. There are three clinical subtypes: congenital lymphedema, which appears shortly after birth; lymphedema praecox, which has its onset at the time of puberty; and lymphedema tarda,

which usually begins after age 35. Familial forms of congenital lymphedema (Milroy's disease) and lymphedema praecox (Meige's disease) may be inherited in an autosomal dominant manner with variable penetrance; autosomal or sex-linked recessive forms are less common. Mutations in genes expressing vascular endothelial growth factor receptor 3 (VEGFR3), which is a determinant of lymphangiogenesis, have been described in patients with Milroy's disease. A mutation on chromosome 15q is associated with the cholestasis-lymphedema syndrome. A mutation in the FOXC2 gene, which encodes a transcription factor that interacts with a signaling pathway involved in the development of lymphatic vessels, has been reported in patients with the lymphedema-distichiasis syndrome, in which lymphedema praecox occurs in patients who also have a double row of eyelashes. A mutation of SOX18, a transcription factor upstream of lymphatic endothelial cell differentiation, has been described in patients with lymphedema, alopecia, and telangiectasias (hypotrichosis, lymphedema, telangiectasia syndrome). Patients with a chromosomal aneuploidy, such as Turner's syndrome, Klinefelter's syndrome, or trisomy 18, 13, or 21, may develop lymphedema. Syndromic vascular anomalies associated with lymphedema include Klippel-Trénaunay syndrome, Parkes-Weber syndrome, and Hennekam's syndrome. Other disorders associated with lymphedema include Noonan's syndrome, yellow nail syndrome, intestinal lymphangiectasia syndrome, lymphangiomyomatosis, and neurofibromatosis type 1.

Secondary lymphedema is an acquired condition that results from damage to or obstruction of previously normal lymphatic channels. Recurrent episodes of bacterial lymphangitis, usually caused by streptococci, are a very common cause of lymphedema. The most common cause of secondary lymphedema worldwide is lymphatic filariasis, affecting approximately 129 million children and adults worldwide and causing lymphedema and elephantiasis in 14 million of these affected individuals. Recurrent bacterial lymphangitis by Streptococcus may result in chronic lymphedema. Other infectious causes include lymphogranuloma venereum and tuberculosis. In developed countries, the most common secondary cause of lymphedema is surgical excision or irradiation of axillary and inguinal lymph nodes for treatment of cancers, such as breast, cervical, endometrial, and prostate cancer, sarcomas, and malignant melanoma. Lymphedema of the arm occurs in 13% of breast cancer patients after axillary node dissection and in 22% after both surgery and radiotherapy. Lymphedema of the leg affects approximately 15% of patients with cancer after inguinal lymph node dissection. Tumors, such as prostate cancer and lymphoma, also can infiltrate and obstruct lymphatic vessels. Less common causes include contact

dermatitis, rheumatoid arthritis, pregnancy, and self-induced or factitious lymphedema after application of tourniquets.

Clinical presentation

Lymphedema is generally a painless condition, but patients may experience a chronic dull, heavy sensation in the leg, and most often they are concerned about the appearance of the leg. Lymphedema of the lower extremity initially involves the foot and gradually progresses up the leg so that the entire limb becomes edematous (Fig. 48-2). In the early stages, the edema is soft and pits easily with pressure. Over time, subcutaneous adipose tissue accumulates, the limb enlarges further and loses its normal contour, and the toes appear square. Thickening of the skin is detected by Stemmer’s sign, which is the inability to tent the skin at the base of the toes. *Peau d’orange* is a term used to describe dimpling of the skin, resembling that of an orange peel, caused by lymphedema. In the chronic stages, the edema no longer pits and the limb acquires a woody texture as the tissues become indurated and fibrotic. The International Society of Lymphology describes four clinical stages of lymphedema (Table 48-3).



FIGURE 48-2
A. Lymphedema characterized by swelling of the leg, nonpitting edema, and squaring of the toes. (Courtesy of Dr. Marie Gerhard-Herman, with permission.) B. Advanced chronic stage of lymphedema illustrating the woody appearance of the leg with acanthosis and verrucous overgrowths. (Courtesy of Dr. Jeffrey Olin, with permission.)

TABLE 48-3

STAGES OF LYMPHEDEMA
Stage 0 (or Ia) A latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist for months or years before overt edema occurs.
Stage I Early accumulation of fluid relatively high in protein content that subsides with limb elevation. Pitting may occur. An increase in proliferating cells may also be seen.
Stage II Limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Late in stage II, the limb may or may not pit as excess fat and fibrosis supervene.
Stage III Lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

Source: Adapted from The 2013 Consensus Document of the International Society of Lymphology: *Lymphology* 46:1, 2013.

Differential diagnosis

Lymphedema should be distinguished from other disorders that cause unilateral leg swelling, such as deep vein thrombosis and chronic venous insufficiency. In the latter condition, the edema is softer, and there is often evidence of a stasis dermatitis, hyperpigmentation, and superficial venous varicosities, as described earlier. Other causes of leg swelling that resemble lymphedema are myxedema and lipedema. Lipedema usually occurs in women and is caused by accumulation of adipose tissue in the leg from the thigh to the ankle with sparing of the feet.

Diagnostic testing

The evaluation of patients with lymphedema should include diagnostic studies to clarify the cause. Abdominal and pelvic ultrasound and computed tomography (CT) can be used to detect obstructing lesions such as neoplasms. Magnetic resonance imaging (MRI) of the affected limb may reveal a honeycomb pattern characteristic of lymphedema in the epifascial compartment and identify enlarged lymphatic channels and lymph nodes. MRI also is useful to distinguish lymphedema from lipedema. Lymphoscintigraphy and lymphangiography are rarely indicated, but either can be used to confirm the diagnosis or differentiate primary from secondary lymphedema. Lymphoscintigraphy involves the injection of radioactively labeled technetium-containing colloid into the distal subcutaneous tissue of the affected extremity, which is imaged with a scintigraphic camera to visualize lymphatic vessels and lymph nodes. Findings indicative of primary lymphedema

include absent or delayed filling of the lymphatic vessels or dermal back flow caused by lymphatic reflux. Findings of secondary lymphedema include dilated lymphatic vessels distal to an area of obstruction. In lymphangiography, iodinated radiocontrast material is injected into a distal lymphatic vessel that has been isolated and cannulated. In primary lymphedema, lymphatic channels are absent, hypoplastic, or ectatic. In secondary lymphedema, lymphatic channels often appear dilated beneath the level of obstruction. The complexities of lymphatic cannulation and the risk of lymphangitis associated with the contrast agent limit the utility of lymphangiography. A novel technique of optical imaging with a near-infrared fluorescence dye may enable quantitative imaging of lymph flow.

TREATMENT Lymphedema

Patients with lymphedema of the lower extremities must be instructed to take meticulous care of their feet to prevent recurrent lymphangitis. Skin hygiene is important, and emollients can be used to prevent drying. Prophylactic antibiotics are often helpful, and fungal infection should be treated aggressively. Patients should be encouraged to participate in physical activity; frequent leg elevation can reduce the amount of edema. Psychosocial support is indicated to assist patients cope with anxiety or depression related to body image, self-esteem, functional disability, and fear of limb loss.

Physical therapy, including massage to facilitate lymphatic drainage, may be helpful. The type of massage used in

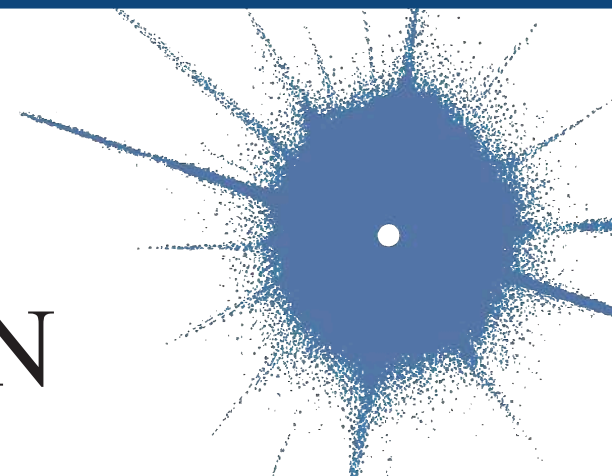
decongestive physiotherapy for lymphedema involves mild compression of the skin of the affected extremity to dilate the lymphatic channels and enhance lymphatic motility. Multilayered, compressive bandages are applied after each massage session to reduce recurrent edema. After optimal reduction in limb volume by decongestive physiotherapy, patients can be fitted with graduated compression hose. Occasionally, intermittent pneumatic compression devices can be applied at home to facilitate reduction of the edema. Diuretics are contraindicated and may cause depletion of intravascular volume and metabolic abnormalities.

Liposuction in conjunction with decongestive physiotherapy may be considered to treat lymphedema, particularly postmastectomy lymphedema. Other surgical interventions are rarely used and often not successful in ameliorating lymphedema. Microsurgical lymphaticovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility.

Therapeutic lymphangiogenesis has been studied in rodent models of lymphedema, but not as yet in humans. Overexpression of vascular endothelial growth factor (VEGF) C generates new lymphatic vessels and improves lymphedema in a murine model of primary lymphedema, and administration of recombinant VEGF-C or VEGF-D stimulated lymphatic growth in preclinical models of postsurgical lymphedema. Clinical trials in patients with lymphedema are required to determine efficacy of gene transfer (cell-based) therapies for lymphedema.

CHAPTER 49

PULMONARY HYPERTENSION



Aaron B. Waxman ■ Joseph Loscalzo

Pulmonary hypertension (PH) is a spectrum of diseases involving the pulmonary vasculature, and is defined as an elevation in pulmonary arterial pressures (mean pulmonary artery pressure >22 mmHg). Pulmonary arterial hypertension (PAH) is a relatively rare form of PH and is characterized by symptoms of dyspnea, chest pain, and syncope. If left untreated, the disease carries a high mortality rate, with the most common cause of death being decompensated right heart failure. There have been significant advances in this field in regard to understanding the pathogenesis, diagnosis, and classification of PAH. Despite these significant advances, there is still a substantial delay in diagnosis of up to 2 years. In many cases, patients whose primary complaint is dyspnea on exertion are frequently misdiagnosed with more common diseases such as asthma or chronic obstructive pulmonary disease. The availability of newer drugs has resulted in a radical change in the management of this disease with significant improvement in both quality of life and mortality. A delay in diagnosis results in an obvious delay in the initiation of appropriate treatment. Clinicians should be able to recognize the signs and symptoms of PH and to complete a systematic workup in patients suspected of having it. In this way, early diagnosis, prompt treatment, and improved outcomes for patients become achievable.

PATHOBIOLOGY

Vasoconstriction, vascular proliferation, thrombosis, and inflammation appear to underlie the development of PAH (**Fig. 49-1**). In long-standing PH, intimal proliferation and fibrosis, medial hypertrophy, and in situ thrombosis characterize the pathologic findings in the pulmonary vasculature. Vascular remodeling at earlier stages may be confined to the small pulmonary arteries. As the disease advances, intimal proliferation and pathologic remodeling progress, resulting in decreased compliance and increased elastance of the pulmonary

vasculature. The outcome is a progressive increase in the right ventricular afterload or total pulmonary vascular resistance (PVR) and, thus, right ventricular work. In subjects with moderate to severe pulmonary vascular disease with significantly increased PVR, as the resting PVR increases, there will be a corresponding increase in mean pulmonary artery pressure (PAP) until the cardiac output (CO) is compromised and starts to fall. With a decline in CO, the PAP will fall. As CO declines as a result of increased afterload and decreased contractility, tachycardia is a compensatory response. Tachycardia decreases filling time and, thus, preload, and results in a reduced fraction of stroke volume available to distend the pulmonary vascular tree.

Abnormalities in multiple molecular pathways and genes that regulate the pulmonary vascular endothelial and smooth muscle cells have been identified (**Table 49-1**). These abnormalities include decreased expression of the voltage-regulated potassium channel, mutations in the bone morphogenetic protein receptor-2, increased tissue factor expression, overactivation of the serotonin transporter, hypoxia-induced activation of hypoxia-inducible factor-1 α , and activation of nuclear factor of activated T cells. As a result, there is a decrease in apoptosis of the smooth muscle cells and the emergence of apoptosis-resistant endothelial cells that promote their accumulation and can obliterate the vascular lumen. In addition, thrombin deposition in the pulmonary vasculature from the prothrombotic state that develops as an independent abnormality or as a result of endothelial dysfunction may amplify vascular cell proliferation and the obliterative arteriopathy.

DIAGNOSIS AND CLASSIFICATION

The diagnosis of PH can be missed without a reasonable index of suspicion. Dyspnea is the most common presenting symptom, but this complaint is far from specific for the diagnosis of PH. PH symptoms are insidious and

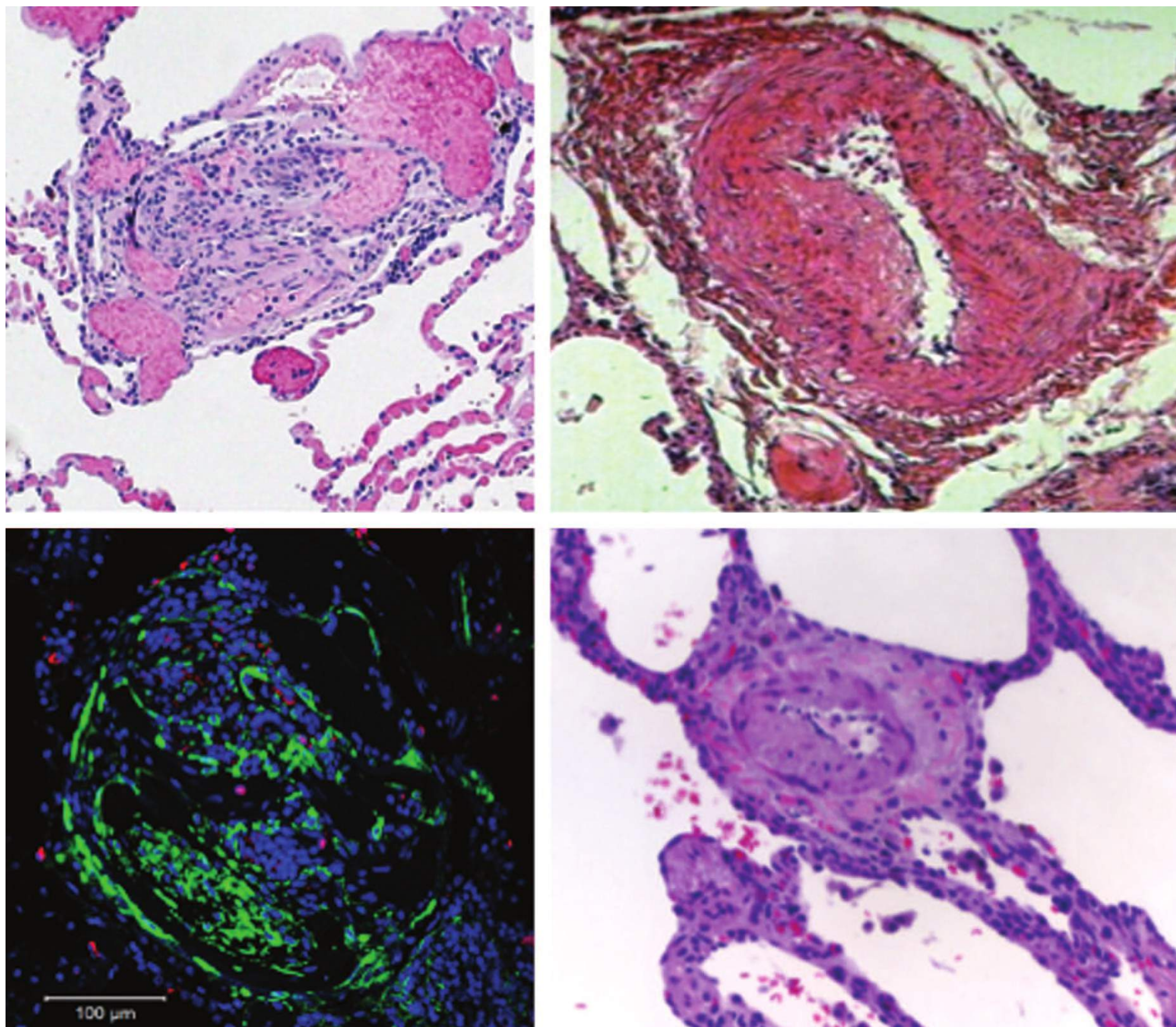


FIGURE 49-1

The left panels show examples of plexogenic pulmonary arteriopathy. These are obstructive and proliferative lesions of the small muscular pulmonary arteries, composed primarily of endothelial cells with intermixed inflammatory cells, myofibroblasts, and connective tissue components. The lower left panel

demonstrates proliferating cells (red PCNA stained cells). Panels on the right demonstrate medial hypertrophy of muscular pulmonary arteries. (Photographs on the left are courtesy of Dr. Stephen Archer, Queen's University School of Medicine, Kingston, Ontario, Canada.)

overlap considerably with many common conditions, including asthma and other lung disease and cardiac disease. The symptoms of PH are often nonspecific and variable. Most patients will present with dyspnea and/or fatigue, whereas edema, chest pain, presyncope, and frank syncope are less common and associated with more advanced disease. On examination, there may be evidence of right ventricular failure with elevated jugular venous pressure, lower extremity edema, and ascites. Additionally, the cardiovascular examination may reveal an accentuated P_2 component of the second heart sound, a right-sided S_3 or S_4 , and a holosystolic tricuspid regurgitant murmur. It is also important to seek signs of the diseases that are often concurrent with PH: clubbing may be seen in some chronic lung diseases, sclerodactyly and telangiectasia may signify scleroderma, and crackles and systemic hypertension may be clues to left-sided systolic or diastolic heart failure.

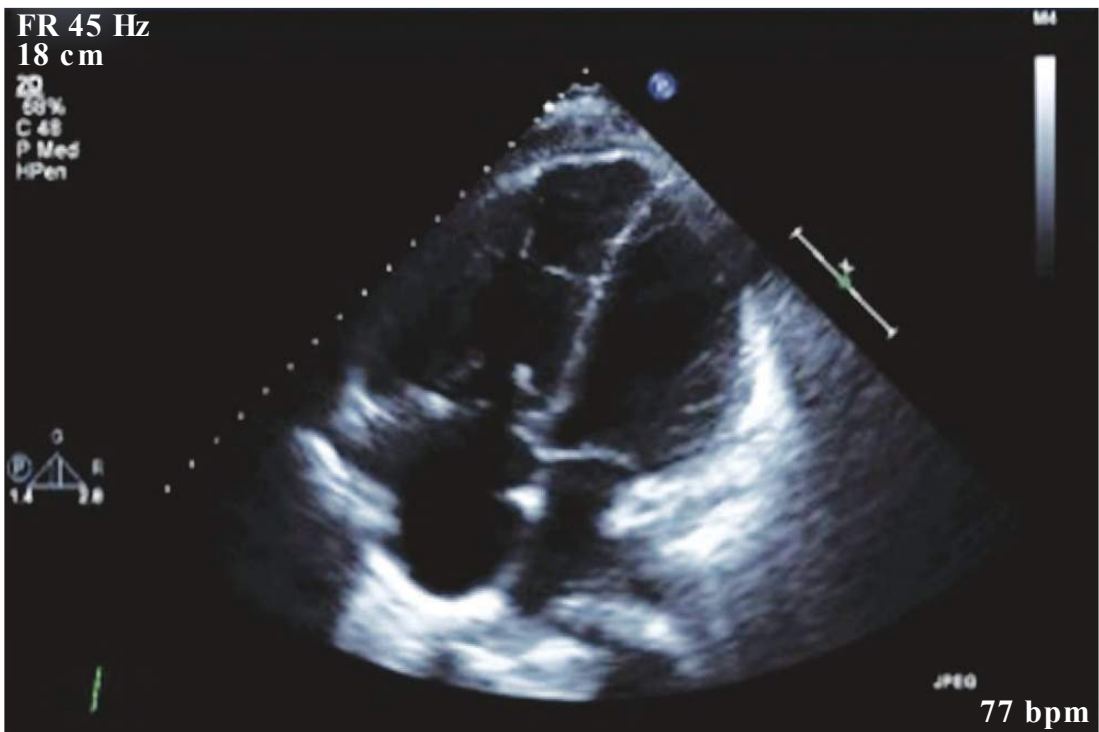
Once clinical suspicion is raised, a systematic approach to diagnosis and assessment is essential. An echocardiogram with (if indicated) a bubble study is the most important screening test. Echocardiography is important for the diagnosis of PH and often essential for determining the cause. All forms of PH may demonstrate a hypertrophied and dilated right ventricle (**Fig. 49-2**) with elevated estimated pulmonary artery systolic pressure. Important additional information can be gleaned about specific etiologies of PH such as valvular disease, left ventricular systolic and diastolic function, intracardiac shunts, and other cardiac diseases.

Although the accuracy of Doppler echocardiography is often debated, a high-quality echocardiogram that is absolutely normal may obviate the need for further evaluation for PH. An echocardiogram is a screening test, whereas invasive hemodynamic monitoring is the gold standard for diagnosis and assessment of disease

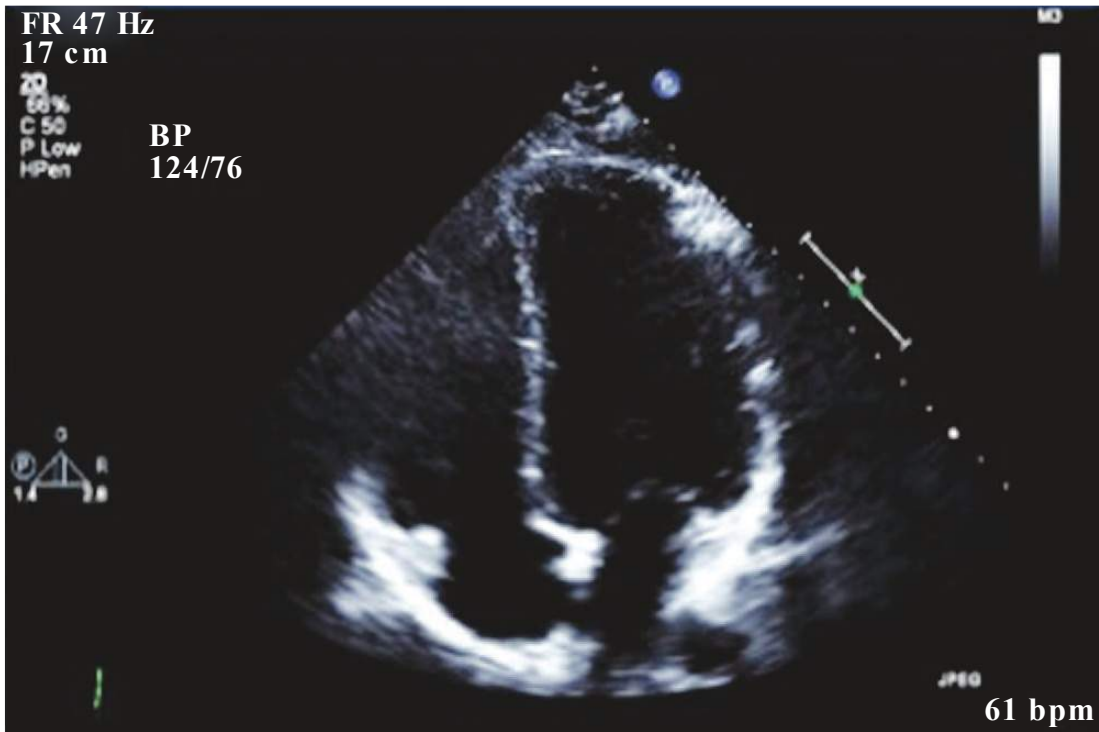
TABLE 49-1

COMPONENTS OF THE PATHOGENESIS OF PULMONARY ARTERIAL HYPERTENSION
Alterations in regulators of proliferation
• Growth factors • Platelet-derived growth factor • Fibroblast growth factor • Vascular endothelial growth factor • Epidermal growth factor • Transforming growth factor β (TGF-β) • Bone morphogenetic protein • Transcription factors • Matrix metalloproteinases • Cytokines • Chemokines • Mitochondria
Alterations in inflammatory mediators
• Altered T cell subsets • Monocytes and macrophages • Interleukin (IL) 1β • IL-6 • MCP-1 • RANTES • Fractalkine
Alterations in vascular tone
• Endothelin • Nitric oxide • Serotonin • Prostaglandin • K⁺ channels • Ca²⁺ channels
Hypoxia-induced remodeling
• HIF-1α • ROS • Mitochondria
TGF- β signaling
• BMPR2 • ALK1 • Endoglin • Smad9 • TGF-β1

Abbreviations: PDGF, platelet-derived growth factor; EGF, epidermal-derived growth factor; FGF, fetal-derived growth factor; VEGF, vascular endothelial-derived growth factor; MCP-1, monocyte chemoattractant protein-1; IL, interleukin.



A



B

FIGURE 49-2

A. Representative echocardiogram showing the apical four-chamber view from a patient with pulmonary hypertension demonstrating an enlarged right atrium and ventricle with some compression of the left side of the heart. B. Same echocardiographic view showing a normal echocardiogram.

severity. With a normal echocardiogram, there may still be some concern for PH; this is particularly true if there is unexplained dyspnea or hypoxemia. In this setting, it is reasonable to proceed to right heart catheterization for definitive diagnosis. Alternatively, if the patient has a reasonable functional capacity, a cardiopulmonary exercise test may help to identify a true physiologic limitation as well as differentiate between cardiac and pulmonary causes of dyspnea. If this test is normal, there is no indication for a right heart catheterization. If a cardiovascular limitation to exercise is found, a right heart catheterization should be pursued.

If the echocardiogram or cardiopulmonary exercise test (CPET) suggests PH and the diagnosis is confirmed by catheterization, a reasonable effort must be made to establish the etiology because this will largely determine the therapeutic approach. A stepwise approach to evaluation is outlined below.

Chest imaging and lung function tests are essential because lung disease is an important cause of PH. A sign of PH that may be evident on chest x-ray include enlargement of the central pulmonary arteries associated with

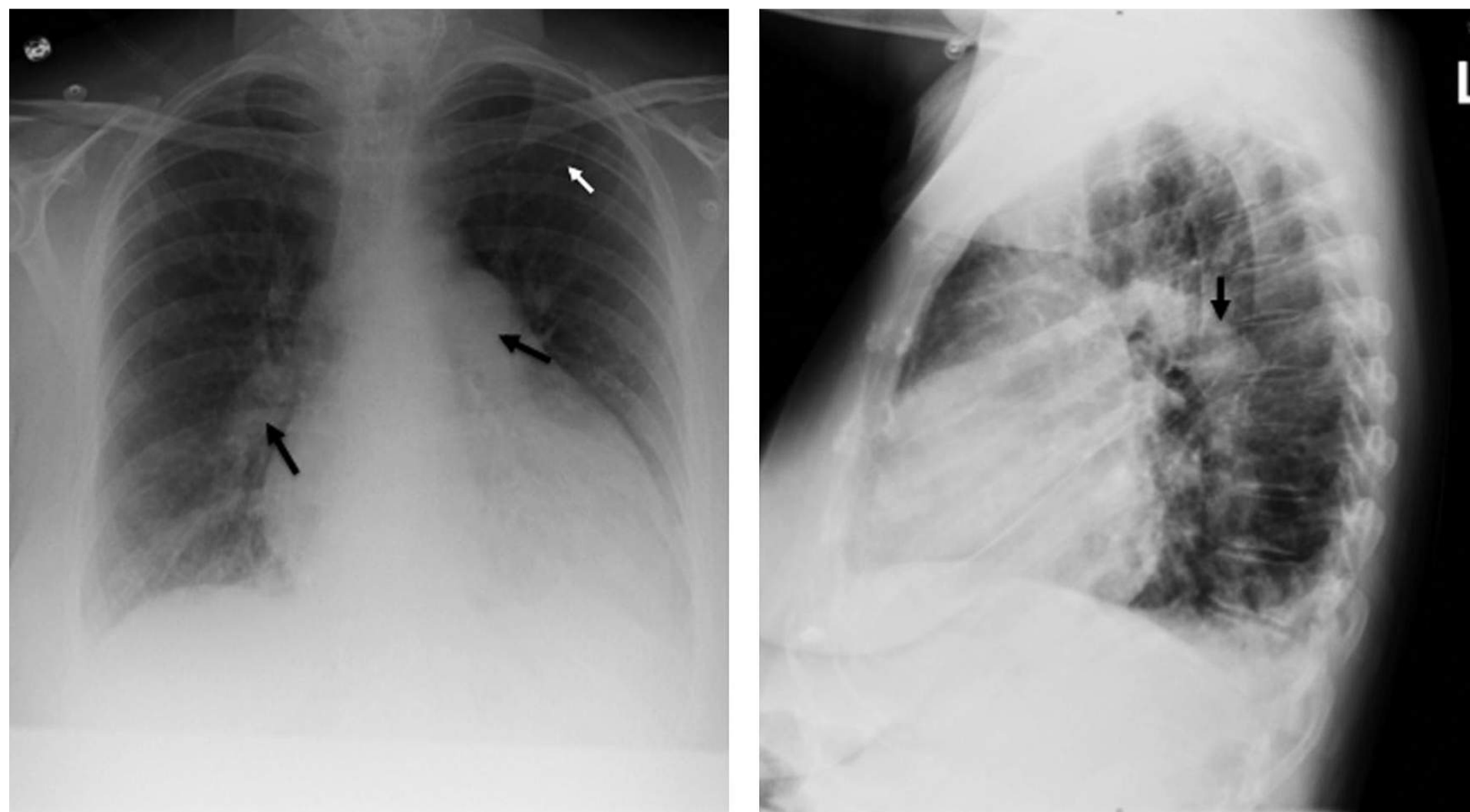


FIGURE 49-3

Posteroanterior (left) and lateral (right) chest radiograph showing enlarged pulmonary arteries (black arrows) and pruning

of the distal pulmonary vasculature (white arrow) commonly seen with advanced pulmonary arterial hypertension.

“vascular pruning,” a relative paucity of peripheral vessels (**Fig. 49-3**). Cardiomegaly, with specific evidence of right atrial and ventricular enlargement, can often be observed. The chest x-ray may also demonstrate significant interstitial lung disease or suggest hyperinflation from obstructive lung disease, which may be the underlying cause or contributor to the development of PH. High-resolution computed tomography (CT) may provide additional useful information. Classic findings of PH on CT include those found on chest x-ray: enlarged pulmonary arteries (**Fig. 49-4**), peripheral pruning of the small vessels, and enlarged right ventricle and atrium. However, high-resolution CT may also reveal signs of venous congestion including centrilobular ground-glass infiltrate and thickened septal lines. In the absence of left heart disease, these findings suggest pulmonary veno-occlusive disease, a rare cause of PAH that can be quite challenging to diagnose.

CT angiograms are commonly used to evaluate acute thromboembolic disease and have demonstrated excellent sensitivity and specificity for that purpose. Ventilation-perfusion (V/Q) scanning has traditionally been used for screening because of its high sensitivity and its role in qualifying patients for surgical intervention. The role of CT angiograms in the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) remains controversial, even with the advent of spiral CT. Although a negative V/Q virtually rules out CTEPH, some cases may be missed through the use of CT angiograms.

Pulmonary function tests are an important component of the evaluation. Although an isolated reduction in DL_{CO} is the classic finding in PAH, results of pulmonary function tests may also suggest restrictive or obstructive lung diseases as the cause of dyspnea or PH.

The 6-minute walk test is also important to evaluate the degree of exertional hypoxemia and limitation and to monitor progression and response to therapy.

Sleep-disordered breathing is another important cause of PH, but a sleep study is generally necessary only when indicated by the patient's history. Nocturnal desaturation is a common finding in PH, even in



FIGURE 49-4

Representative computed tomography scan of the chest demonstrating enlarged main pulmonary arteries. There is also a mosaic pattern evident in both lungs.

the absence of sleep-disordered breathing. Thus, all patients should undergo nocturnal oximetry screening, regardless of whether classic symptoms of obstructive sleep apnea or obesity-hypoventilation syndrome are observed. Laboratory tests that are important for screening include an HIV test when clinically indicated. In addition, all patients should have antinuclear antibodies, rheumatoid factor, and scl-70 antibodies assessed to screen for the most common rheumatologic diseases associated with PH if clinically indicated. Liver function and hepatitis serology tests are important to screen for underlying liver disease. Finally, there is an increasing role for brain natriuretic peptide (BNP) testing in the diagnosis and management of PH. BNP and the N-terminus of its propeptide (NT-proBNP) correlate with right ventricular function, hemodynamic severity, and functional status in PAH.

Right heart catheterization with pulmonary vasodilator testing remains the gold standard both to establish the diagnosis of PH and to enable selection of appropriate medical therapy. The definition of precapillary PH or PAH requires (1) an increased mean pulmonary artery pressure (mPAP ≥ 25 mmHg); (2) a pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure ≤ 15 mmHg; and (3) PVR > 3 Wood units. Postcapillary PH is differentiated from precapillary PH by a PCWP of ≥ 15 mmHg; this is further differentiated into passive, based on a transpulmonary gradient < 12 mmHg, or reactive, based on a transpulmonary gradient > 12 mmHg and an increased PVR. In either case, the CO may be normal or reduced.

Vasodilators with a short duration of action, such as inhaled nitric oxide, inhaled epoprostenol, or intravenous adenosine, are preferred for vasodilator testing. A decrease in mPAP by ≥ 10 mmHg to an absolute level of ≤ 40 mmHg without a decrease in CO is defined as a positive pulmonary vasodilator response, and responders are considered for long-term treatment with calcium channel blockers (CCBs). Less than 12% of patients are deemed vasoreactive during testing, and even fewer exhibit long-term responsiveness to CCBs. Acute vasodilator-induced reductions in PVR and mPAP predict better long-term survival even among patients not treated with CCBs. The need for invasive hemodynamic measurements to diagnose PH accurately poses an additional problem when evaluating older patients. Physicians are often reluctant to refer older patients for invasive procedures. However, the diagnosis of PH is increasing in the older population, at least in part because of increased awareness of this disease in the elderly and increased use of screening echocardiograms. Furthermore, the increased availability of oral and less complicated therapeutic options has encouraged the referral of older patients for evaluation and treatment.

PULMONARY HYPERTENSION AS A COMORBID DISEASE

PAH is just one of a number of disease classifications that affect the pulmonary vascular bed. PH was previously classified as primary or secondary, but as understanding of the various contributing diseases has increased, classification systems have attempted to group these diseases by clinical features to aid in diagnosis. The World Health Organization (WHO) formulated a clinical classification of the various manifestations of PH, of which PAH is a subgroup, according to similarities in pathophysiologic mechanisms and clinical presentation. PH is a diverse mix of pathologies in which the only unifying theme is elevated PAP relative to left atrial pressure. The categorization of PH was designed by convenience for the purpose of facilitating novel treatments to be tested across different presentations and is not based on a molecular understanding of the pathology and is not a guide for management decisions.

The current classification system, last revised in 2013 during the Fifth World Symposium on Pulmonary Hypertension, recognizes five categories of PH, including PAH, PH due to left heart disease, PH due to chronic lung disease, PH associated with chronic thromboemboli, and a group of miscellaneous diseases that only rarely cause PH.

Pulmonary arterial hypertension

WHO Group I PH, pulmonary arterial hypertension (PAH), is a relatively rare cause of PH. PAH includes a group of diseases that result in pulmonary arterial precapillary remodeling marked by intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion, and classic plexiform lesions. PAH is defined as a sustained elevation in resting mPAP ≥ 25 mmHg, PVR > 240 dyne·s/cm⁵, and PCWP or left ventricle end-diastolic pressure of ≤ 15 mmHg based on a right heart catheterization. With a normal PCWP and an elevated mPAP, these diseases demonstrate an increased transpulmonary gradient (mPAP – PCWP); in addition, the PVR is elevated.

Idiopathic pulmonary arterial hypertension (IPAH) is a progressive disease that leads to right heart failure and death. It is typically seen in young women. The National Institutes of Health registry, the first large registry of patients with PAH, reported that the average age at diagnosis was 36 years, with only 9% of patients with IPAH over the age of 60 at diagnosis. However, the more current clinical data suggest that the patient demographics are changing. The Pulmonary Hypertension Connection registry found that the average age of diagnosis for IPAH was 45 years, with 8.5% of patients older than 70 years at diagnosis. This finding is

supported by data from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), the largest cohort of PAH to date, which reported that the average age at diagnosis of IPAH was 44.9 ± 0.6 years.

Other forms of PAH that deserve specific consideration in patients are those associated with HIV, connective tissue disease, and portal hypertension. Although HIV is a rare cause of PAH, this form of PAH is indistinguishable from IPAH and is an important cause of mortality in the HIV-infected population. Importantly, there is no correlation between the stage of HIV infection and the development of PAH.

Among connective tissue diseases, the prevalence of PAH has been established only for systemic sclerosis, especially in those with limited cutaneous scleroderma. Although the average age of scleroderma onset is 30 to 50 years old, patients who eventually develop scleroderma-associated PAH tend to be older at the time of scleroderma diagnosis. Outcomes of scleroderma are closely linked to the development of PAH and are associated with a poor prognosis, although modern therapies have improved outcomes.

Portopulmonary hypertension occurs in 2–10% of patients with established portal hypertension. Its occurrence appears to be independent of the cause of liver disease and is observed in patients with nonhepatic causes of portal hypertension. A hyperdynamic circulatory state is common, as in most patients with advanced liver disease; however, the same pulmonary vascular remodeling observed in other forms of PAH is seen in the pulmonary vascular bed in portopulmonary hypertension. It is important to distinguish this process from hepatopulmonary syndrome, which can also manifest with dyspnea and hypoxemia but is pathophysiologically distinct from portopulmonary hypertension in that abnormal vasodilation of the pulmonary vasculature leads to intrapulmonary shunting.

Pulmonary hypertension associated with left heart disease

WHO Group II PH includes patients with left heart systolic failure, aortic and mitral valve disease, and heart failure with preserved ejection fraction (HFpEF). PH can develop as a result of all of these conditions. The hallmark of Group II PH (i.e., PH due to left heart disease) is elevated left atrial pressure with resulting pulmonary venous hypertension. In general, the transpulmonary gradient and PVR remain normal. Although this phenomenon is well described in both left-sided valvular disease and left-sided systolic heart failure, studies suggest that HFpEF may carry a higher overall risk of PH.

Whatever the cause of elevated left atrial pressure (i.e., systolic or diastolic heart failure or valvular disease), the increased pulmonary venous pressure

indirectly leads to a rise in pulmonary arterial pressure. The presence of PH portends a poor prognosis in all forms of heart failure. In particular, chronic pulmonary venous hypertension may lead to a reactive pulmonary arterial vasculopathy, seen as an elevated transpulmonary gradient (>12 mmHg) and elevated PVR (>3 Wood units). Pathologically, this process is marked by pulmonary arteriolar remodeling with intimal fibrosis and medial hyperplasia akin to that seen in PAH.

Pulmonary hypertension associated with lung disease

Intrinsic lung disease is the second most common cause of PH, although its actual prevalence is difficult to ascertain. PH has been observed in both chronic obstructive lung disease and interstitial lung disease. It can also be seen in diseases with mixed obstructive/restrictive physiology: bronchiectasis, cystic fibrosis, mixed obstructive restrictive disease marked by fibrosis in the lower lung zones, and emphysema predominantly in the upper lung zones. As in patients with left heart disease, PH associated with chronic lung disease is usually modest; however, some of these patients appear to have PH “out of proportion” to their parenchymal lung disease, suggesting intrinsic pulmonary arterial disease. These patients typically have more severe PH, with results of pulmonary function tests demonstrating a very low DL_{CO} .

Although PH is described in most forms of interstitial lung disease, it has been most extensively studied in idiopathic pulmonary fibrosis; however, the individual studies have been small. Early echocardiographic data suggested that the prevalence of PH in interstitial lung diseases was high, but invasive hemodynamic monitoring suggests that the incidence is considerably lower than originally believed. The diagnosis of PH portends poor outcome in pulmonary fibrosis.

Also included in Group III PH is sleep-disordered breathing. Sleep apnea has long been associated with PH. However, PH associated with sleep-disordered breathing is generally mild.

Pulmonary hypertension associated with chronic thromboembolic disease

The development of PH after chronic thromboembolic obstruction of the pulmonary arteries is well described, but its incidence is not known. The incidence of PH after a single pulmonary embolic event is thought to be quite low and likely increases following recurrent embolism. The risk factors for developing CTEPH are unclear. Many patients have no history of clinical venous thromboembolism. The pathogenesis of CTEPH is poorly understood. Obstruction of the proximal pulmonary vasculature is important and often the dominant factor; however, additional pulmonary vascular remodeling

occurs. Approximately 10–15% of patients will develop a disease very similar clinically and pathologically to PAH after resection of the proximal thrombus.

OTHER DISORDERS AFFECTING THE PULMONARY VASCULATURE

Sarcoidosis

Patients with sarcoidosis can develop PH as a result of lung involvement. Consequently, patients with sarcoidosis who present with progressive dyspnea and PH require a thorough evaluation. Although the majority of sarcoidosis patients with PH generally do not respond to therapy for PAH, a subset of patients with sarcoidosis and severe PH do have a beneficial response to therapy.

Sickle cell disease

Cardiovascular system abnormalities are prominent in the clinical spectrum of sickle cell disease, including PH. The etiology is multifactorial, including hemolysis, hypoxemia, thromboembolism, chronic high CO, and chronic liver disease. The presence of PH in patients with sickle cell disease is rare.

Schistosomiasis

Globally, schistosomiasis is one of the most common causes of PH. The development of PH occurs in the setting of hepatosplenic disease and portal hypertension. Studies suggest that inflammation from the infection triggers the pulmonary vascular changes that occur. The diagnosis is confirmed by finding the parasite ova in the urine or stool of patients with symptoms, which can be difficult. The efficacy of therapies directed toward PH in these patients is unknown.

PHARMACOLOGIC TREATMENT OF PAH

PH was a consistently fatal condition with no effective medical treatment options before 1996; however, since that time, there has been an upsurge in the development of novel therapeutic agents for PAH. There are several approved agents for PAH, including prostacyclin and prostacyclin analogues, phosphodiesterase-5 inhibitors, a soluble guanylyl cyclase stimulator, and endothelin receptor antagonists, that have improved the outlook dramatically. Although there is no cure for PAH, current pharmacologic therapies improve morbidity and, in some cases, mortality.

PROSTANOIDS

In PAH, endothelial dysfunction and platelet activation cause an imbalance of arachidonic acid metabolites

with reduced prostacyclin levels and increased thromboxane A₂ production. Prostacyclin (PGI₂) activates cyclic adenosine monophosphate (cAMP)-dependent pathways that mediate vasodilation. PGI₂ also has antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation. Protein levels of prostacyclin synthase are decreased in pulmonary arteries of patients with PAH. The imbalance of mediators is addressed by the exogenous administration of prostanoids as therapy in advanced PAH.

Epoprostenol was the first prostanoid available for the management of PAH. Epoprostenol delivered as a continuous intravenous infusion improves functional capacity and survival in PAH. The efficacy of epoprostenol in WHO functional class 3 and 4 PAH patients was demonstrated in a clinical trial that showed improved quality of life, mPAP, PVR, 6-minute walk distance (6MWD), and mortality. Treprostinil has a longer half-life than epoprostenol (~4 h vs ~6 min), which allows for continuous subcutaneous and intravenous administration. Treprostinil has been shown to improve pulmonary hemodynamics, symptoms, exercise capacity, and survival in PAH.

Inhaled prostacyclins provide the beneficial effects of infused prostacyclin therapy without the inconvenience and side effects (risk of infection and infusion site reactions) of infusion catheters. Both inhaled iloprost and treprostinil have been approved for patients with WHO class 3 and 4 PAH. The main advantage of treprostinil is less frequent administration. Inhaled formulations can be efficacious in moderately symptomatic patients with PAH and may be appropriate when used in combination with an oral medication. Phosphodiesterase-5 (PDE5) inhibitors (e.g., sildenafil) increase cyclic guanosine monophosphate (cGMP) levels and activate cGMP-dependent signaling pathways that also mediate vasodilation and platelet inhibition. Thus, the addition of a PDE5 inhibitor augments the pulmonary hemodynamic and functional capacity benefits of prostanoids in PAH.

Endothelin receptor antagonists

Endothelin receptor antagonists (ERAs) target endothelin-1 (ET-1), a potent endogenous vasoconstrictor and vascular smooth muscle mitogen that is elevated in PAH patients. Endothelin levels are increased coincident with increased PVR and mPAP and decreased CO and 6MWD.

ERAs block the binding of ET-1 to either endothelin receptor A (ET-A) and/or B (ET-B). ET-A receptors found on pulmonary artery smooth muscle cells mediate vasoconstriction. In the normal pulmonary vasculature, ET-B receptors are found on endothelial cells and mediate vasodilation via production of prostacyclin and nitric oxide as well as

ET-1 clearance. Three ERAs approved for use in the United States are bosentan and macitentan both, nonselective receptor antagonists, and ambrisentan, a selective ET-A receptor antagonist.

Studies have shown that both bosentan and macitentan improve hemodynamics and exercise capacity and delay clinical worsening. The randomized, placebo-controlled, phase III Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 comparing bosentan with placebo demonstrated improved symptoms, 6MWD, and WHO functional class. The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients (EARLY) comparing bosentan with placebo demonstrated improved PVR and 6MWD.

Several studies, including the phase III, placebo-controlled Ambrisentan in Pulmonary Arterial Hypertension-1 (ARIES-1) trial, suggest that ambrisentan improves exercise tolerance, WHO functional class, hemodynamics, and quality of life in patients with PAH. There are no trial data to evaluate whether the selective ET-A receptor antagonism of ambrisentan has any advantage over the nonselective ET receptor antagonism of bosentan.

Phosphodiesterase type-5 inhibitors

Nitric oxide derived from endothelial cells activates guanylyl cyclase, which, in turn, generates cGMP in vascular smooth muscle cells and platelets. cGMP is a second messenger that induces vasodilation through relaxation of the arterial smooth muscle cells and inhibits platelet activation. PDE5 enzymes metabolize cGMP. Therefore, cGMP PDE5 inhibitors prolong the vasodilatory effect of nitric oxide, especially within the pulmonary arterial bed where high concentrations of cGMP are found. There are currently two PDE5 inhibitors used for the treatment of PAH, sildenafil and tadalafil. Both agents have been shown to improve hemodynamics and 6MWD. Recently, the oral soluble guanylyl cyclase stimulator, riociguat, was approved for the treatment of both PAH and CTEPH.

Unmet and future research needs in pulmonary hypertension

Presently there are only three classes of therapy for patients with PAH, and even with therapy, the median survival for a person with PAH is only 5–6 years (Table 49-2).

TABLE 49-2

FDA-APPROVED THERAPIES FOR THE TREATMENT OF PAH			
GENERIC NAME	ROUTE OF ADMINISTRATION	DRUG CLASS	INDICATION
Epoprostenol	IV	Prostacyclin derivative	Treatment of PAH to improve exercise capacity
Iloprost	Inhaled	Prostacyclin derivative	Treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration
Treprostinil	IV or SC	Prostacyclin derivative	Treatment of PAH to diminish symptoms associated with exercise
Treprostinil	Inhaled	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Treprostinil	Oral	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Bosentan	Oral	Non-selective endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and to decrease clinical worsening
Ambrisentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Macitentan	Oral	Non-selective endothelin antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Sildenafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise capacity and delay clinical worsening
Tadalafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise ability
Riociguat	Oral	Soluble guanylyl cyclase stimulator	Treatment of PAH to improve exercise capacity and delay clinical worsening

Abbreviations: FDA, U.S. Food and Drug Administration; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDES, phosphodiesterase-5.

Although there are five subtypes of PH, current approved therapies only address one subtype. Not only do we need to expand the treatment options for patients with PAH, we also need to develop effective therapies for all patients with PH. Limited survival is, in part, a result of delay in diagnosis. Improved awareness among clinicians and patients could lead to more timely diagnosis that will affect the response to therapy and survival. PH needs to be diagnosed in a timely manner so

that therapy can be initiated as soon as possible. Patients should also have the option of referral to a specialty center that focuses on treatment of patients with pulmonary vascular disease, which will ensure their access to state-of-the-art care and a multidisciplinary approach to care. Finally, there need to be continued efforts at developing new therapies that target the increasingly complex and overlapping pathways involved in the various forms of PH.

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SECTION VI

CARDIOVASCULAR ATLASES

CHAPTER 50

ATLAS OF ELECTROCARDIOGRAPHY

Ary L. Goldberger

The electrocardiograms (ECGs) in this atlas supplement those illustrated in **Chap. 11**. The interpretations emphasize findings of specific teaching value.

All of the figures are from ECG Wave-Maven, Copyright 2003, Beth Israel Deaconess Medical Center, <http://ecg.bidmc.harvard.edu>.

The abbreviations used in this chapter are as follows:

- AF—atrial fibrillation
- HCM—hypertrophic cardiomyopathy

- LBBB—left bundle branch block
- LVH—left ventricular hypertrophy
- MI—myocardial infarction
- RBBB—right bundle branch block
- RV—right ventricular
- RVH—right ventricular hypertrophy
- SR—sinus rhythm

MYOCARDIAL ISCHEMIA AND INFARCTION

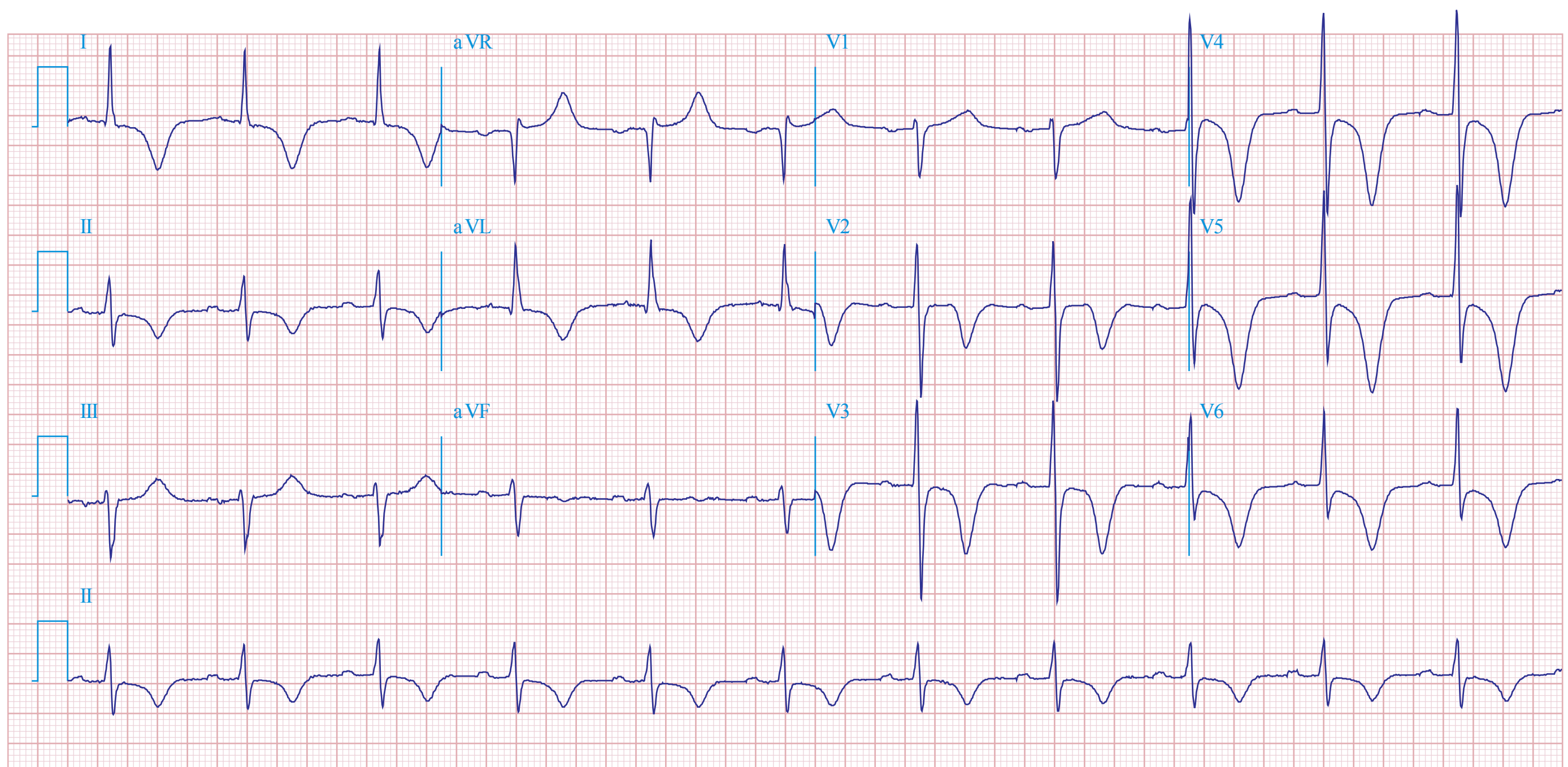


FIGURE 50-1

Anterior wall ischemia (deep T-wave inversions and ST-segment depressions in I, aVL, V₃–V₆) in a patient with LVH (increased voltage in V₂–V₅).

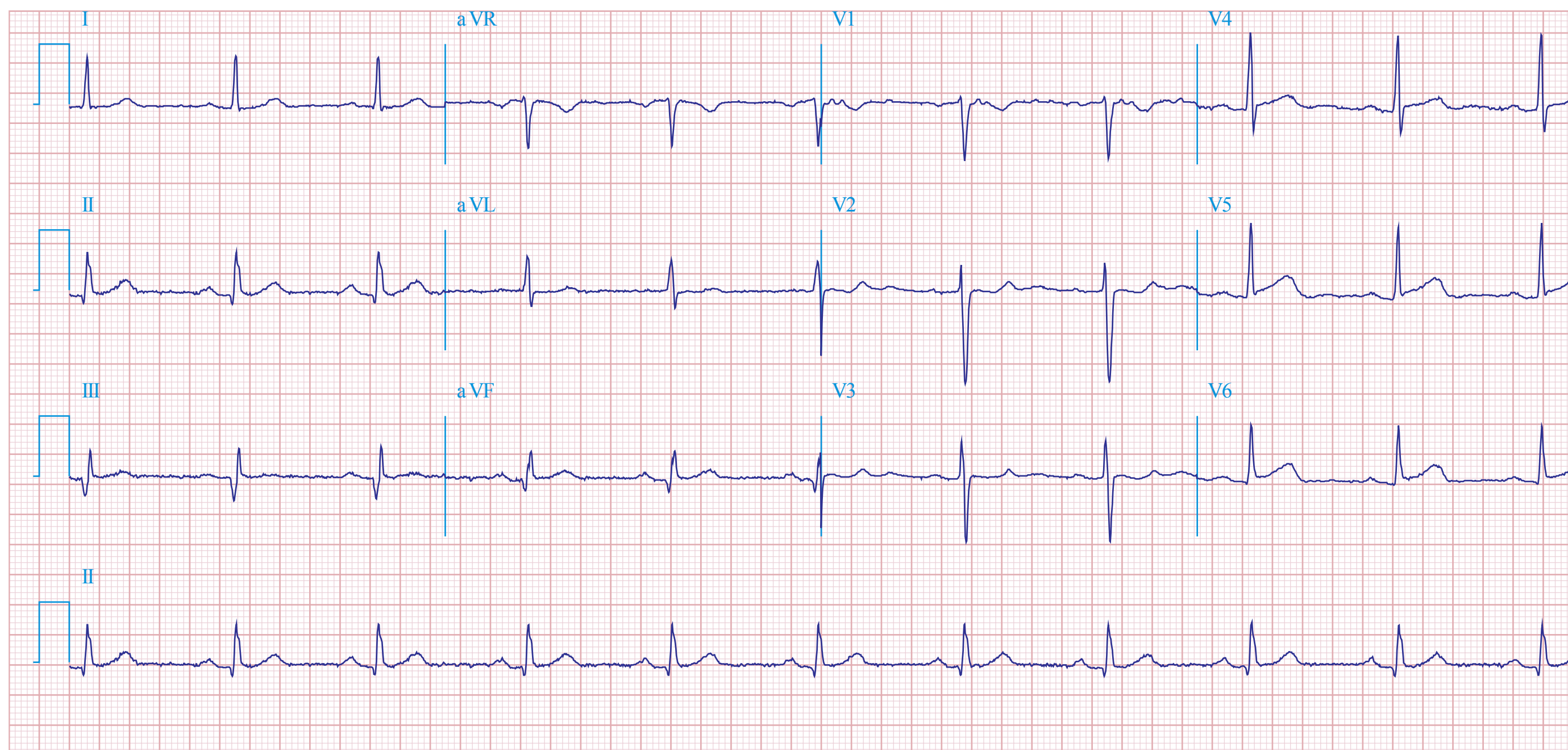


FIGURE 50-2

Acute anterolateral wall ischemia with ST elevations in V_4 – V_6 . Probable prior inferior MI with Q waves in leads II, III, and aVF.

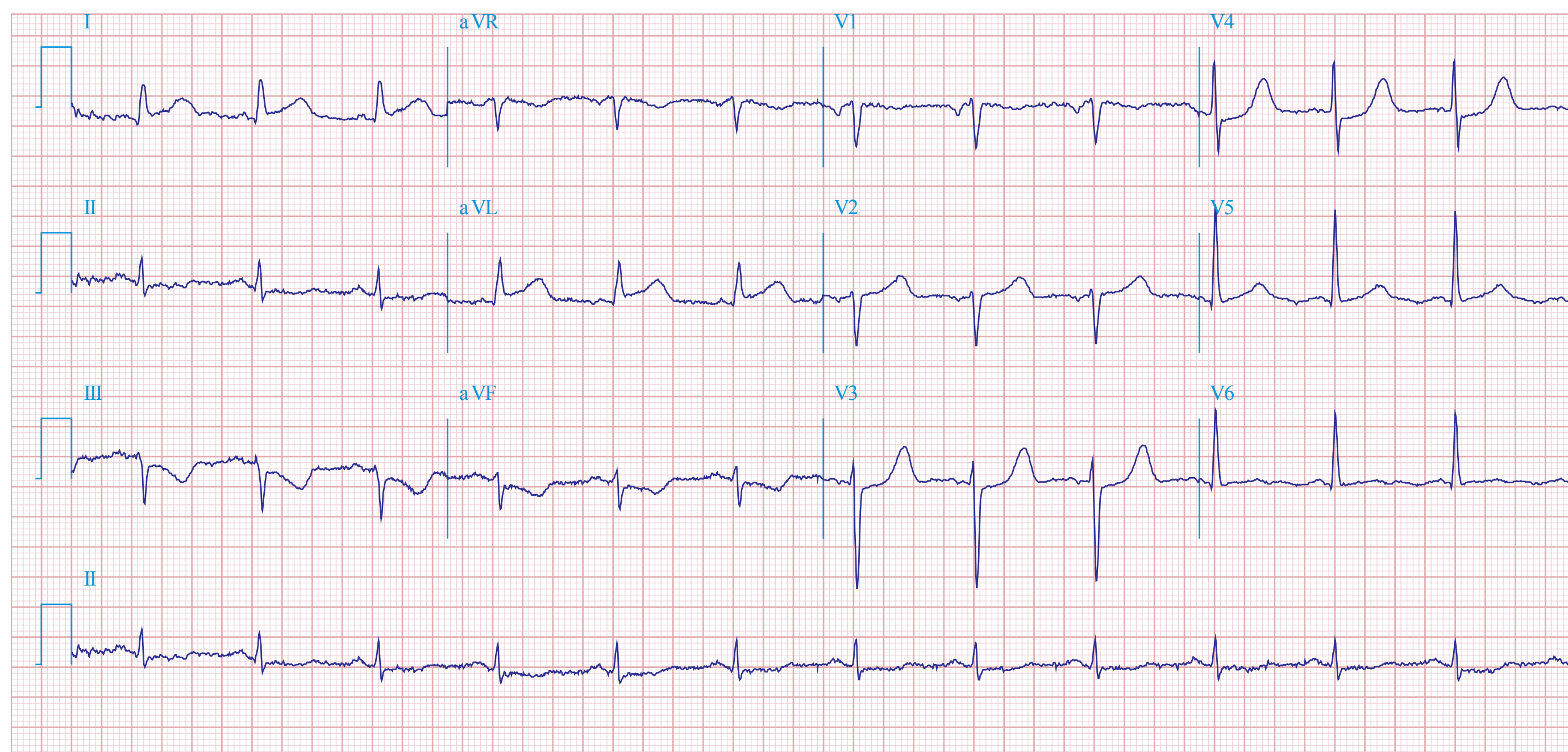


FIGURE 50-3

Acute lateral ischemia with ST elevations in I and aVL with probable reciprocal ST depressions inferiorly (II, III, and aVF). Ischemic ST depressions also in V_3 and V_4 . Left atrial abnormality.

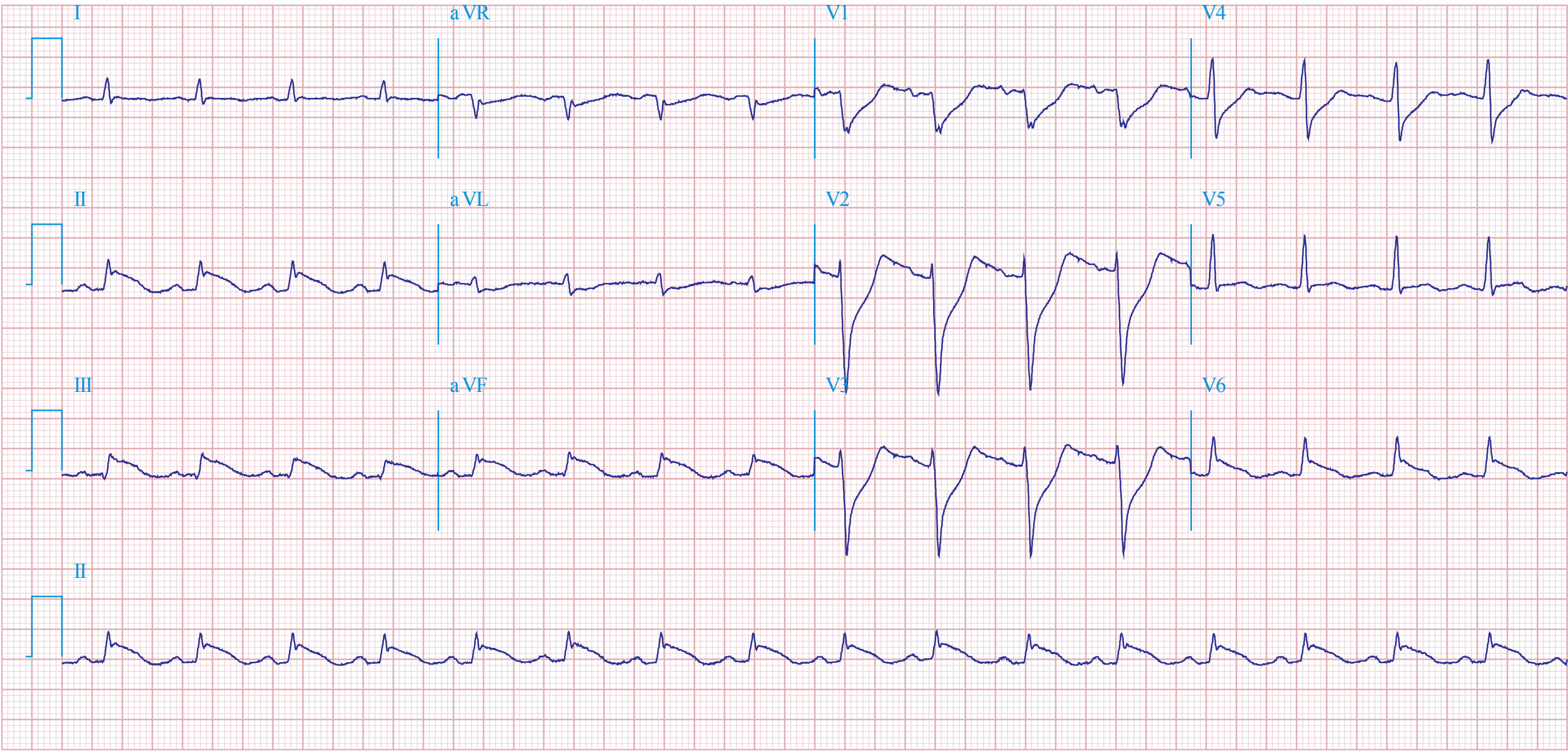


FIGURE 50-4
Sinus tachycardia. Marked ischemic ST-segment elevations in inferior limb leads (II, III, aVF) and laterally (V₆) suggestive of acute inferolateral MI, and prominent ST-segment depressions with upright T waves in V₁–V₄ are consistent with associated acute posterior MI.

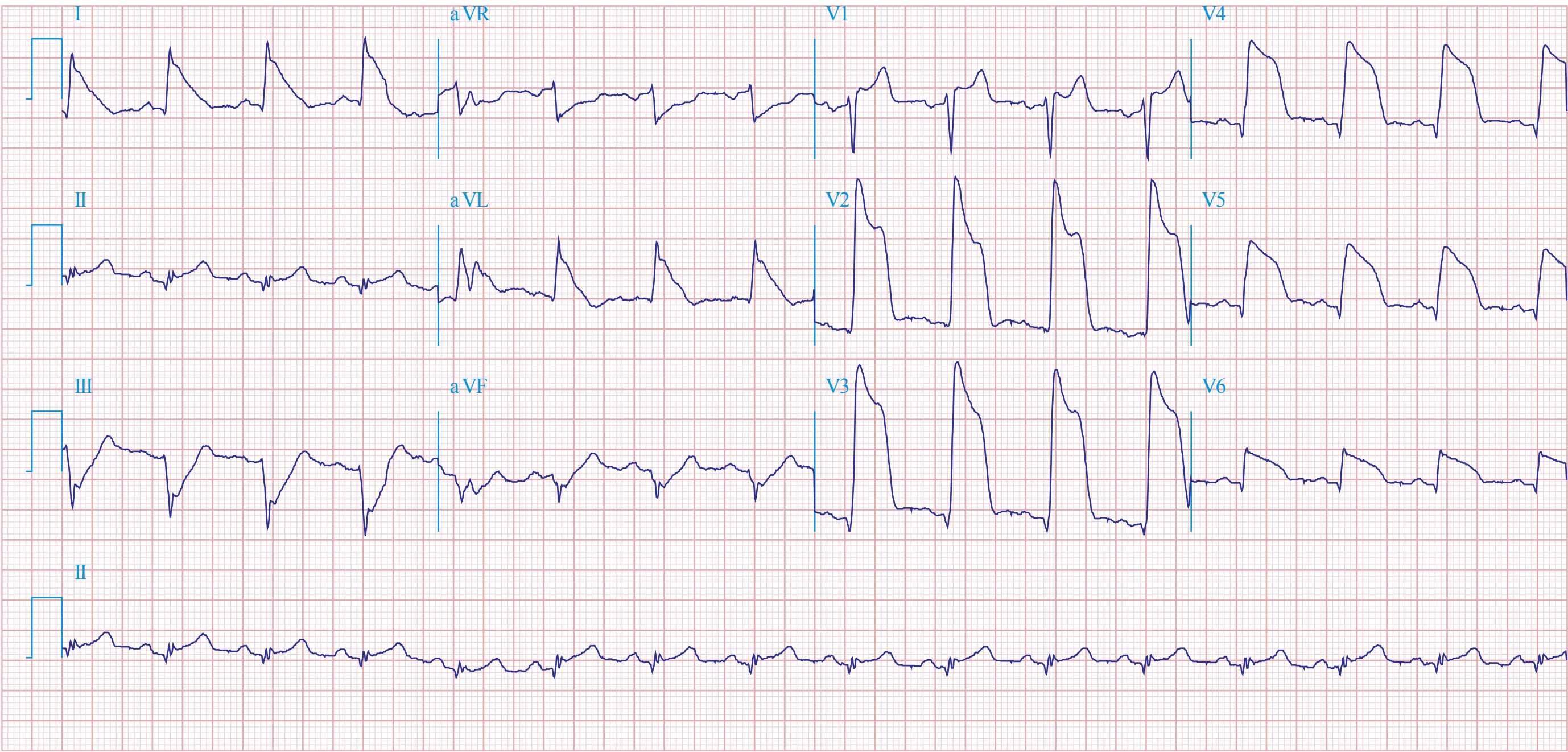


FIGURE 50-5
Acute, extensive anterior MI with marked ST elevations in I, aVL, V₁–V₆ and low amplitude pathologic Q waves in V₃–V₆. Marked reciprocal ST-segment depressions in III and aVF.

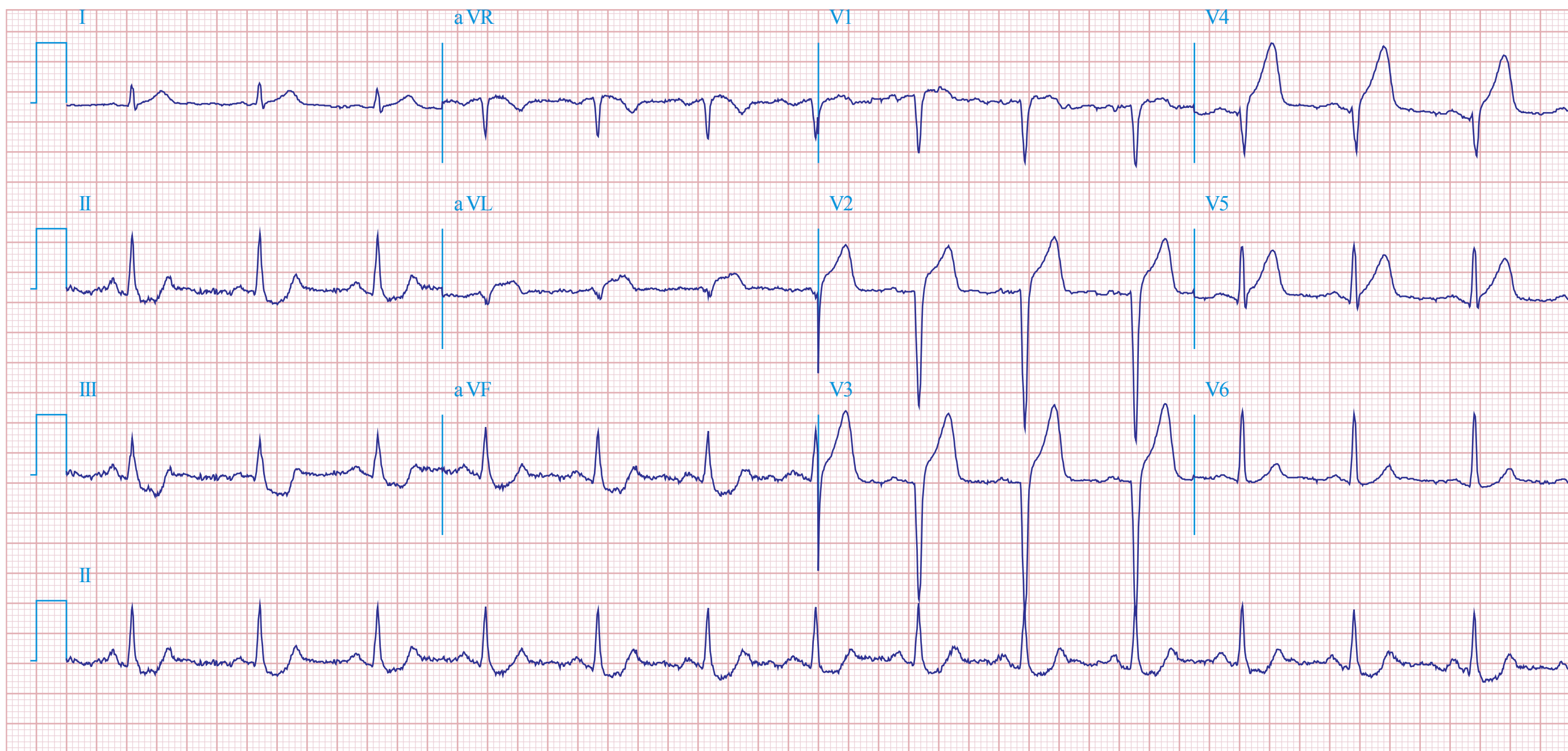


FIGURE 50-6

Acute anterior wall MI with ST elevations and Q waves in V_1 – V_4 and aVL and reciprocal inferior ST depressions.

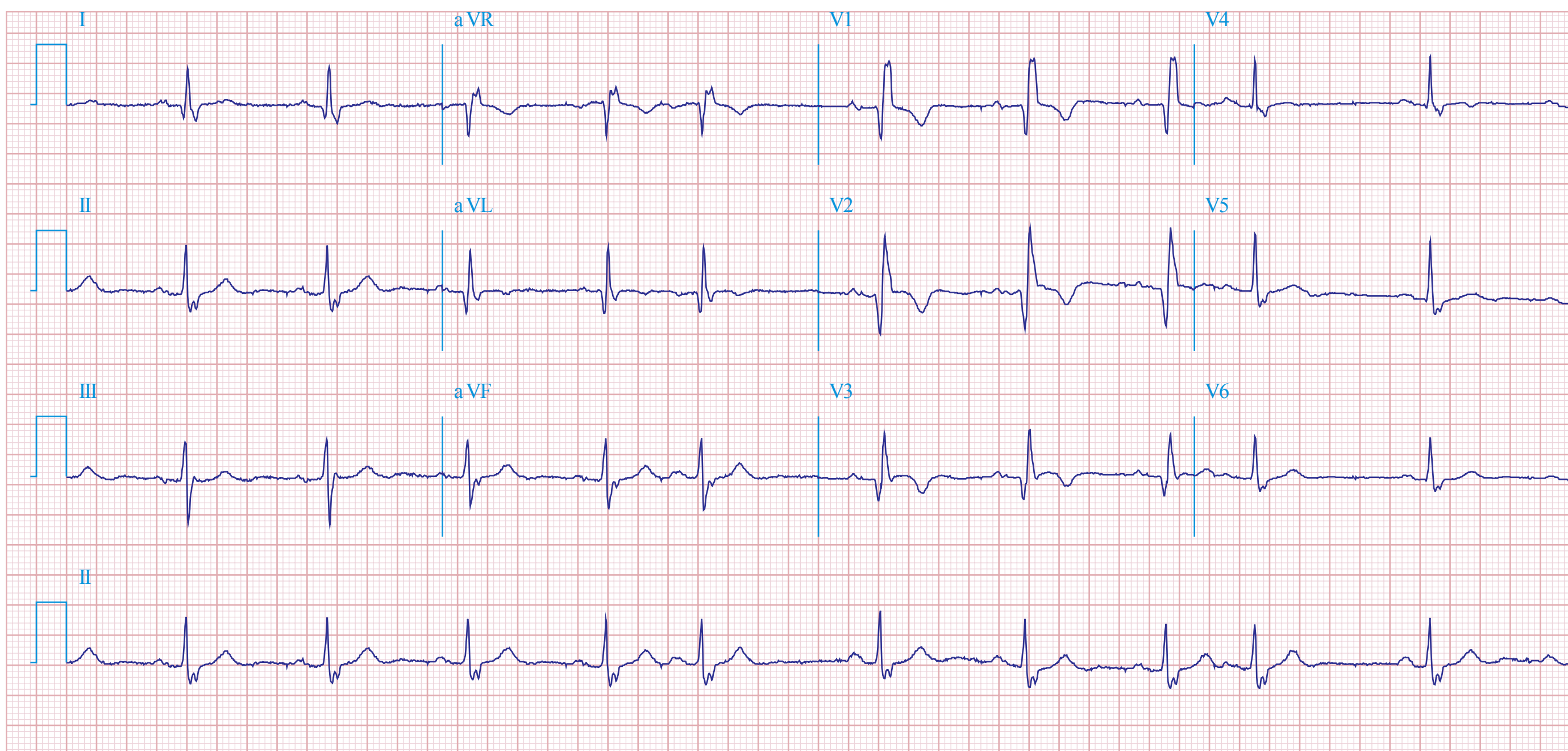


FIGURE 50-7

SR with premature atrial complexes. RBBB; pathologic Q waves and ST elevation due to acute anterior/septal MI in V_1 – V_3 .

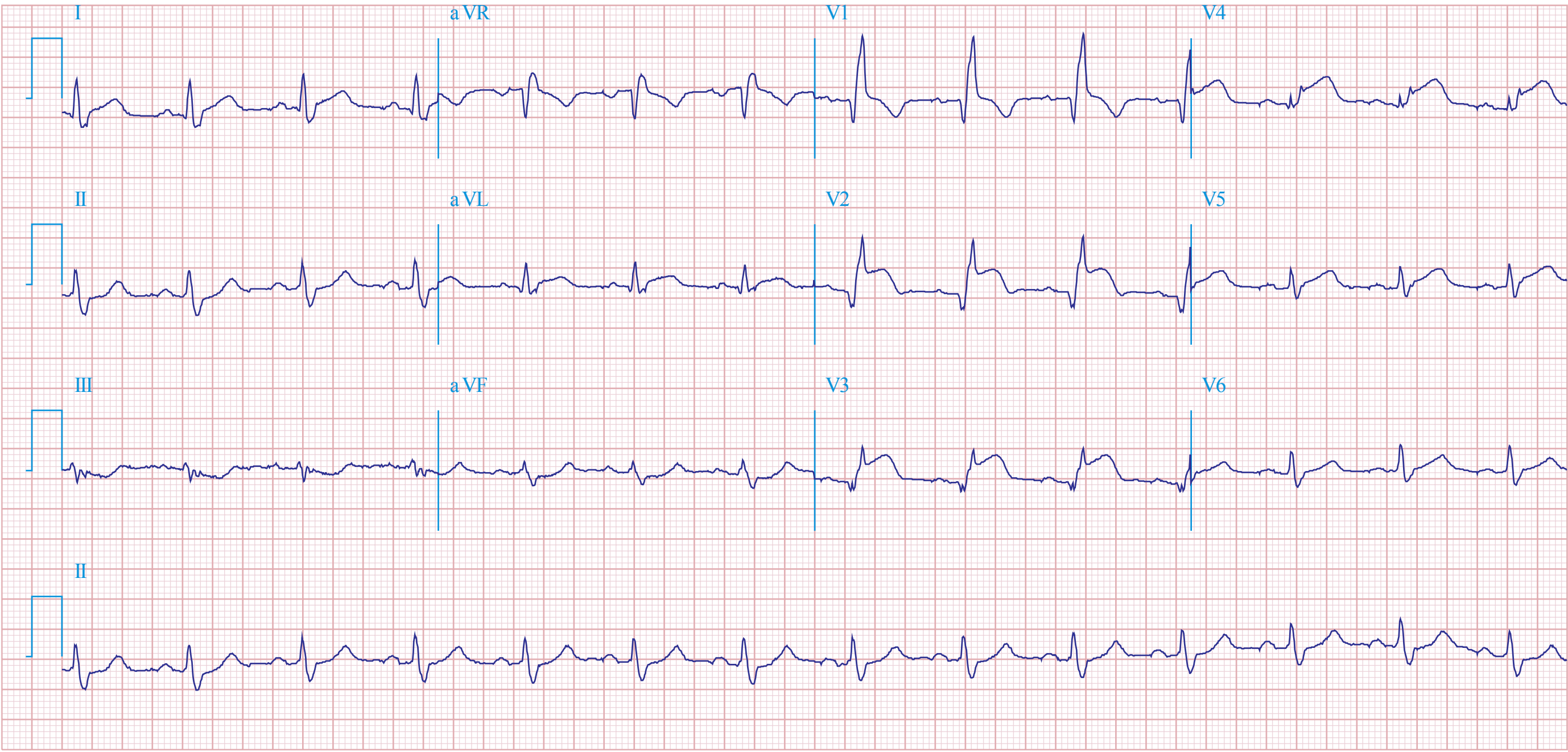


FIGURE 50-8
Acute anteroseptal MI (Q waves and ST elevations in V₁–V₄) with RBBB (note terminal R waves in V₁).

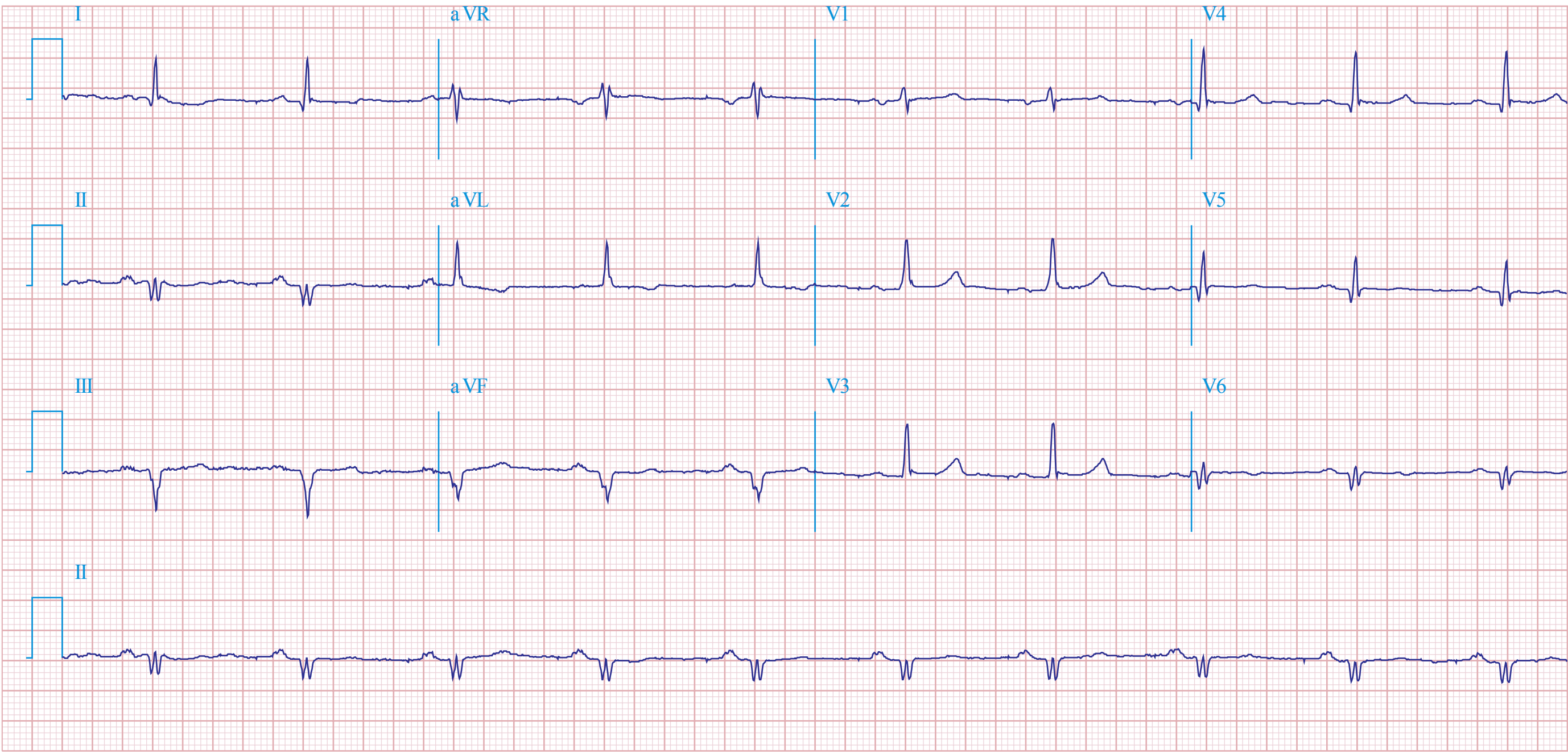


FIGURE 50-9
Extensive prior MI involving inferior-posterior-lateral wall (Q waves in leads II, III, aVF, tall R waves in V₁, V₂, and Q waves in V₅, V₆). T-wave abnormalities in leads I and aVL, V₅, and V₆.

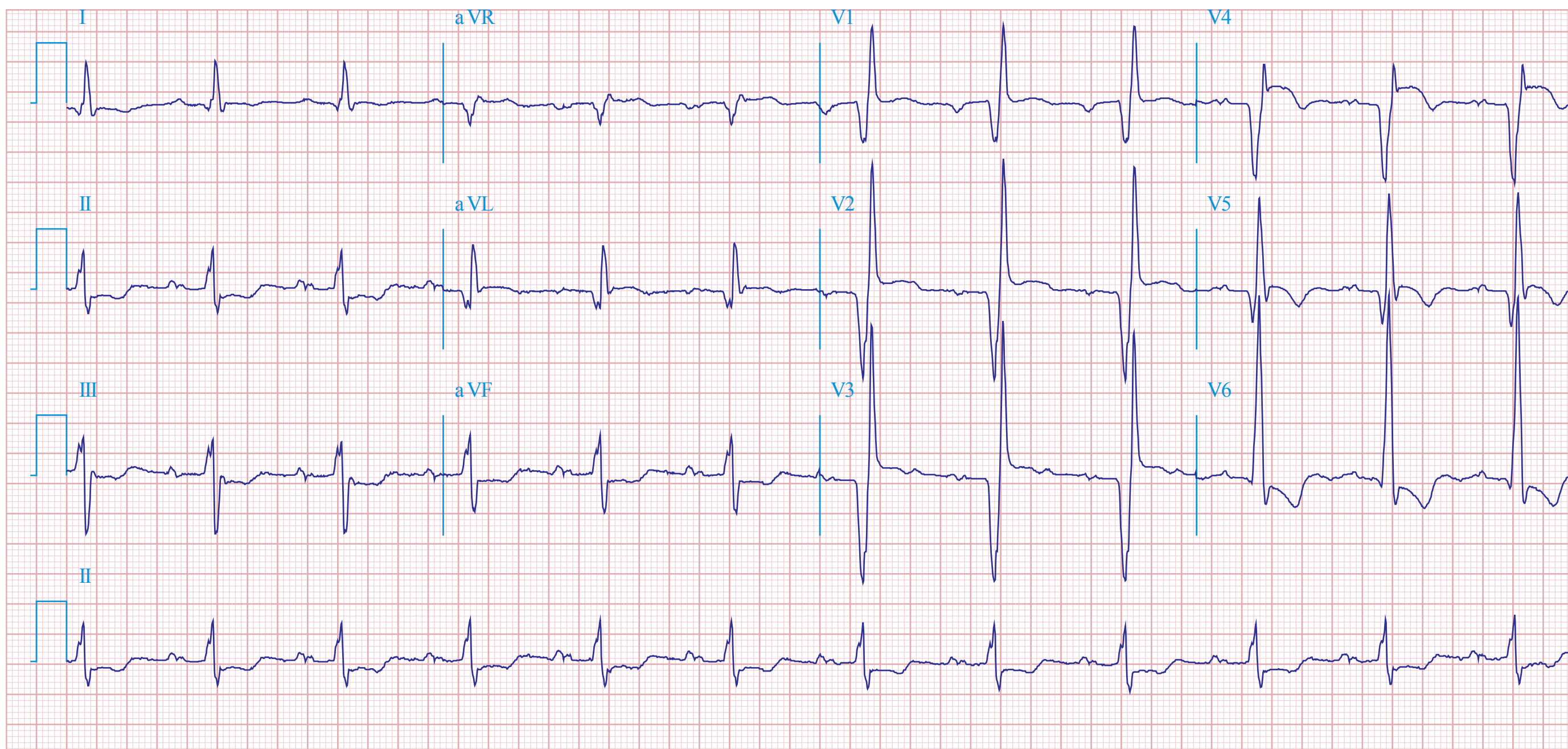


FIGURE 50-10

SR with PR prolongation (“first-degree AV block”), left atrial abnormality, LVH, and RBBB. Pathologic Q waves in V_1 – V_5 and aVL with ST elevations (a chronic finding in this

patient). Findings compatible with prior anterolateral MI and left ventricular aneurysm.

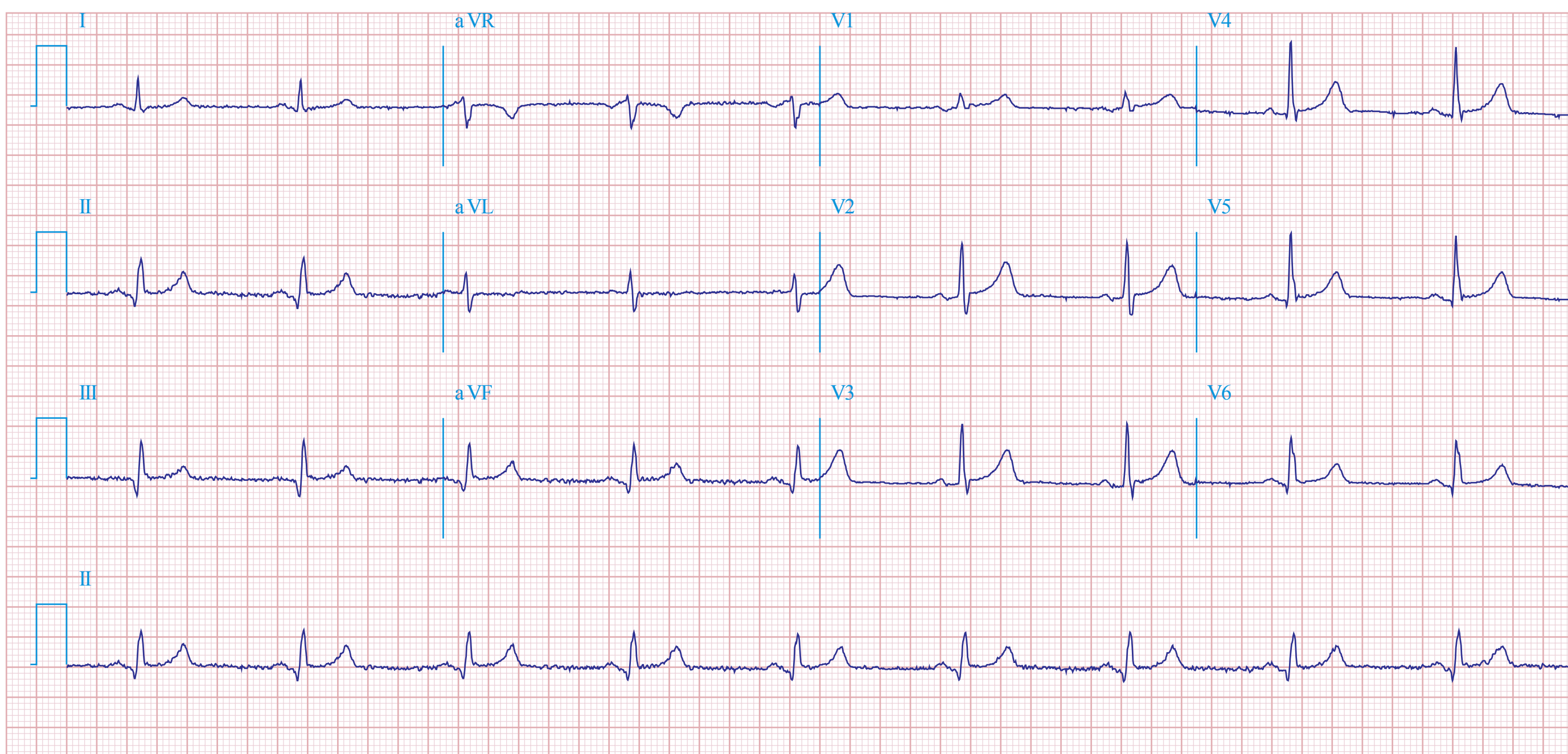


FIGURE 50-11

Prior inferior-posterior MI. Wide (0.04 s) Q waves in the inferior leads (II, III, aVF); broad R wave in V_1 (a Q wave “equivalent”

here). Absence of right-axis deviation and the presence of upright Twaves in V_1 – V_2 are also against RVH.

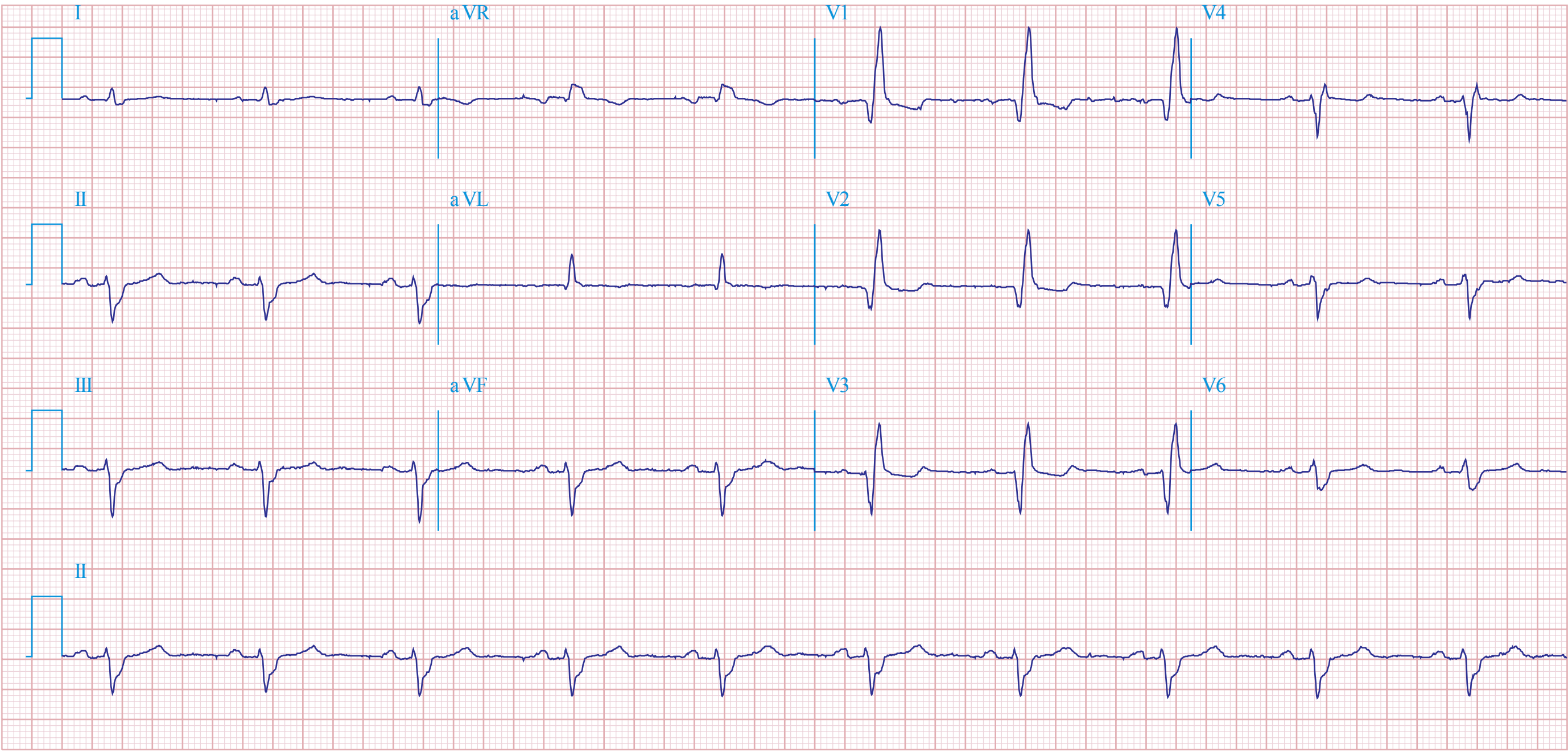


FIGURE 50-12
SR with RBBB (broad terminal R wave in V₁) and left anterior fascicular block (hemiblock) and pathologic anterior Q waves in V₁–V₃. Patient had severe multivessel coronary artery disease, with echocardiogram showing septal dyskinesis and apical akinesis.

PERICARDITIS

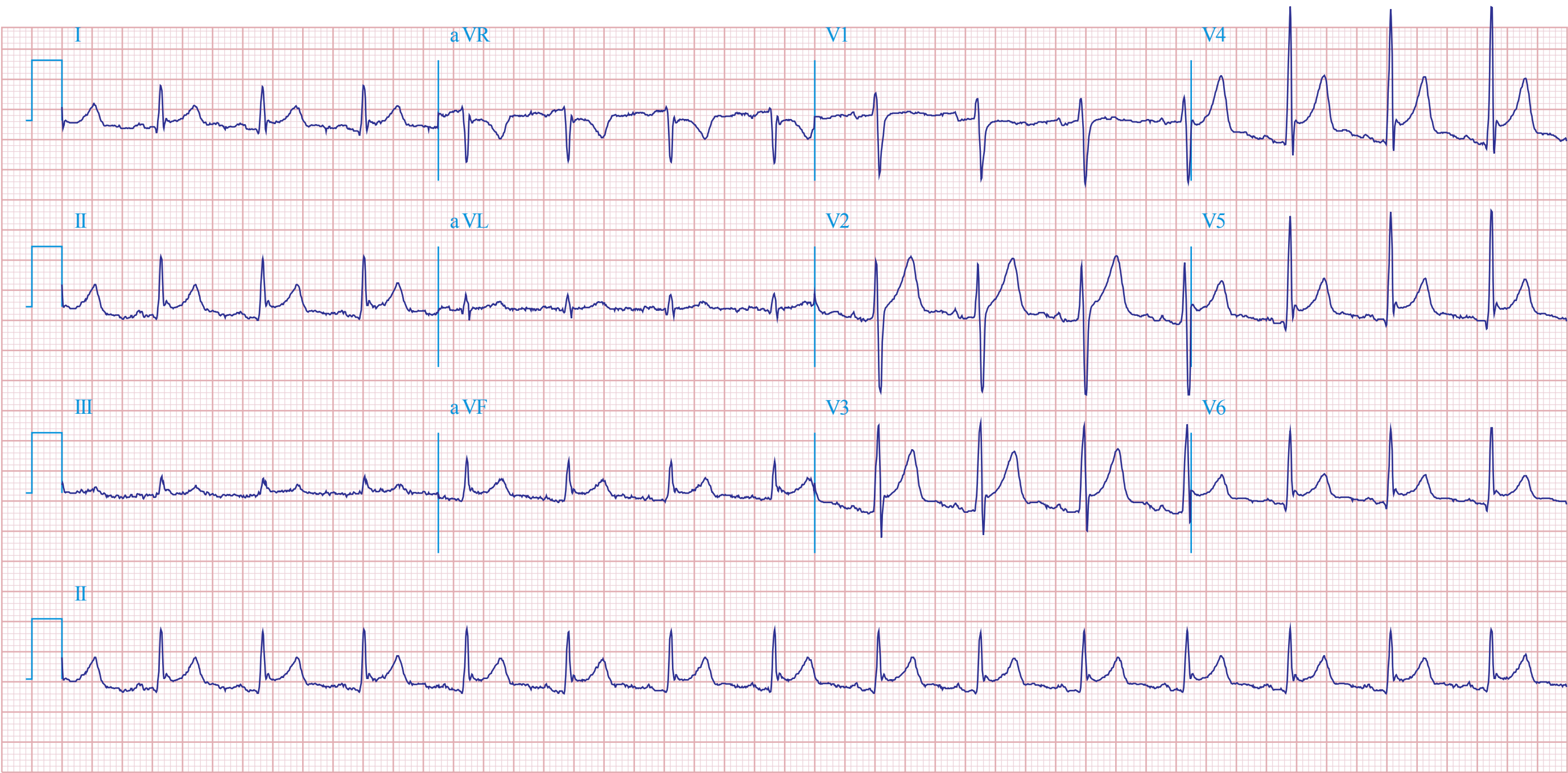


FIGURE 50-13
Acute pericarditis with diffuse ST elevations in I, II, III, aVF, V₃–V₆, without T-wave inversions. Also note concomitant PR-segment elevation in aVR and PR depression in the inferolateral leads.

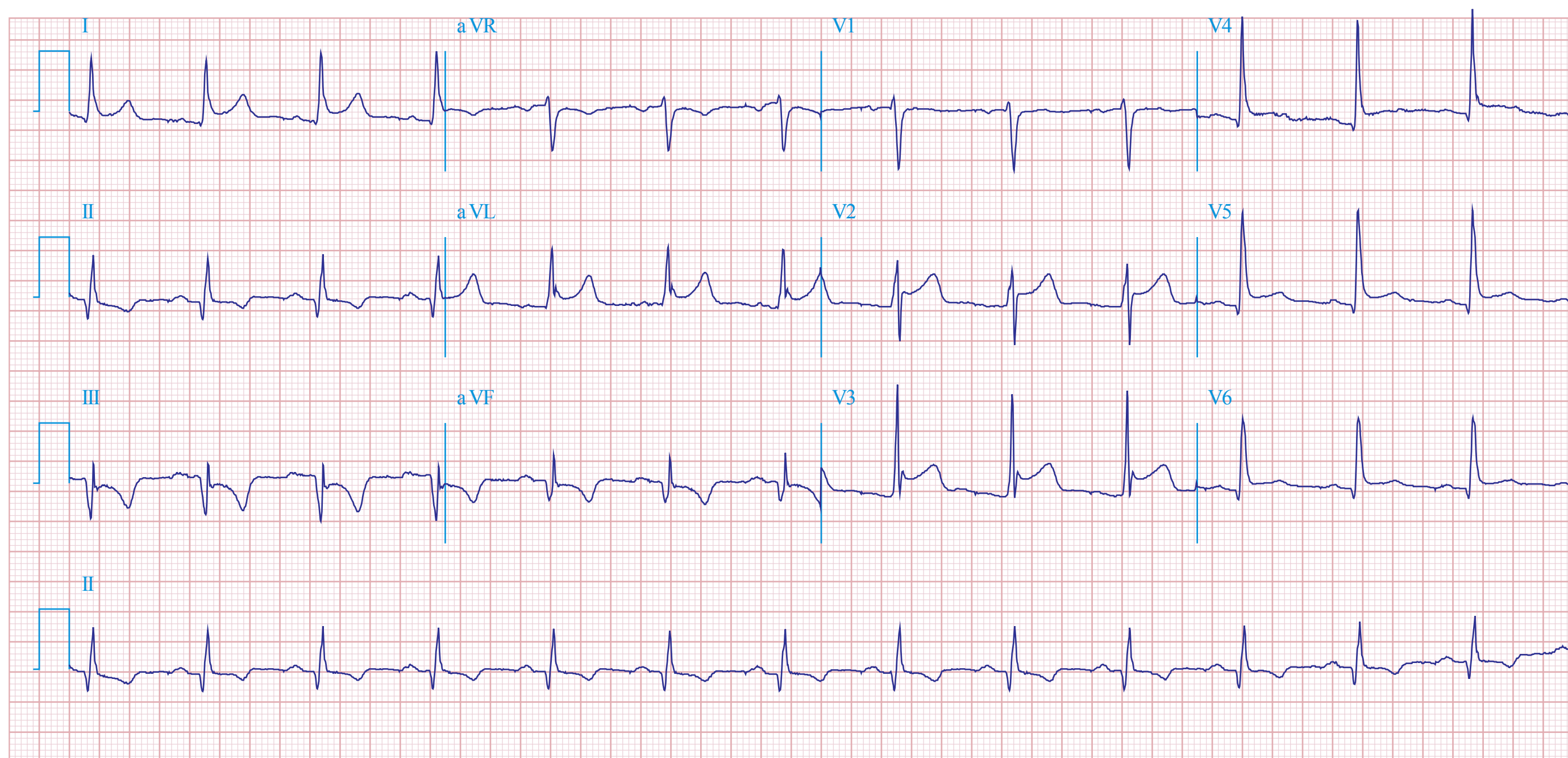


FIGURE 50-14

SR; diffuse ST elevations (I, II, aVL, aVF, V₂–V₆) with associated PR deviations (elevated PR in aVR; depressed in V₄–V₆);

borderline low voltage. Q-wave and T-wave inversions in II, III, and aVF. Diagnosis: acute pericarditis with inferior Q-wave MI.

VALVULAR HEART DISEASE AND HYPERTROPHIC CARDIOMYOPATHY

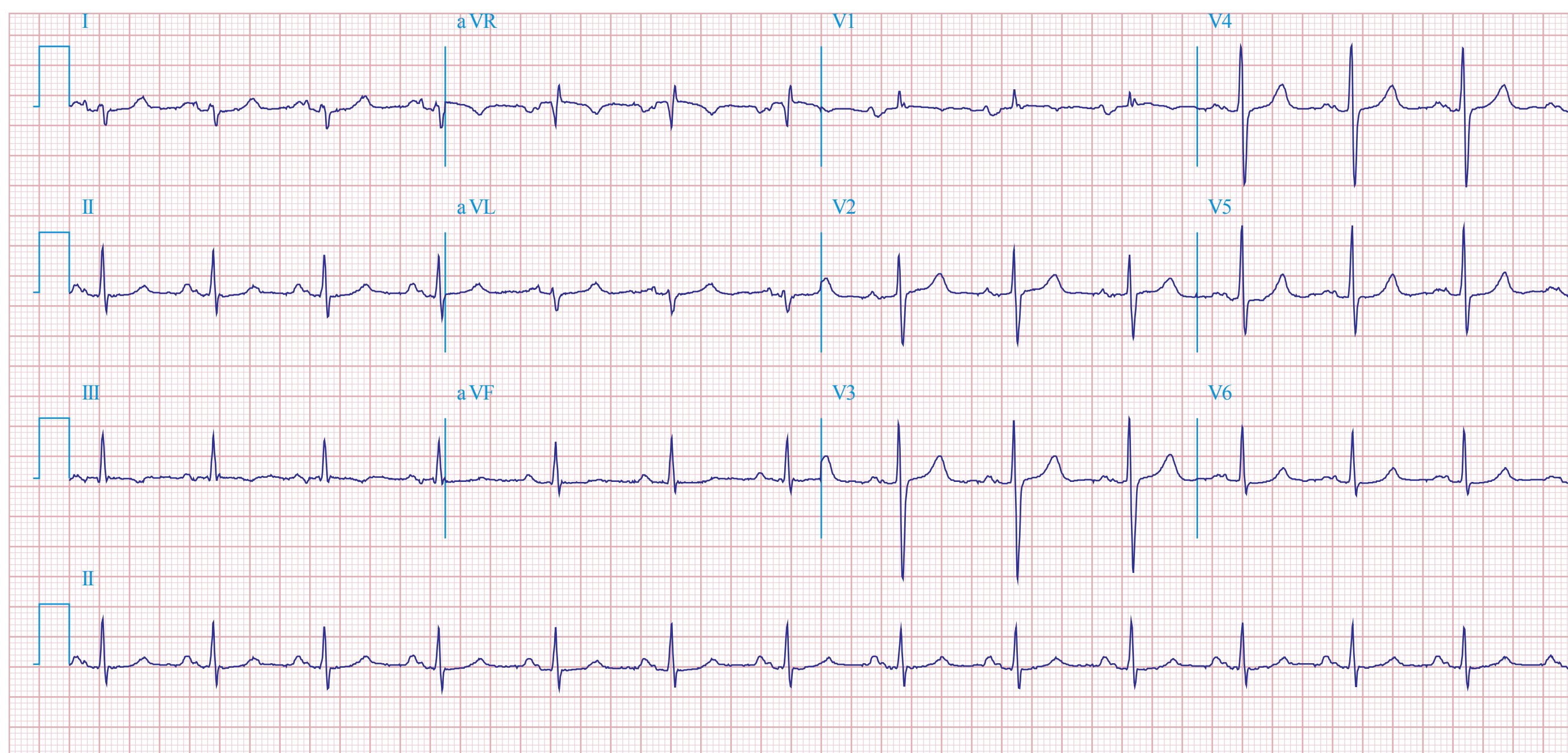


FIGURE 50-15

SR, prominent left atrial abnormality (see I, II, V₁), right-axis deviation, and RVH (tall, relatively narrow R wave in V₁) in a patient with mitral stenosis.

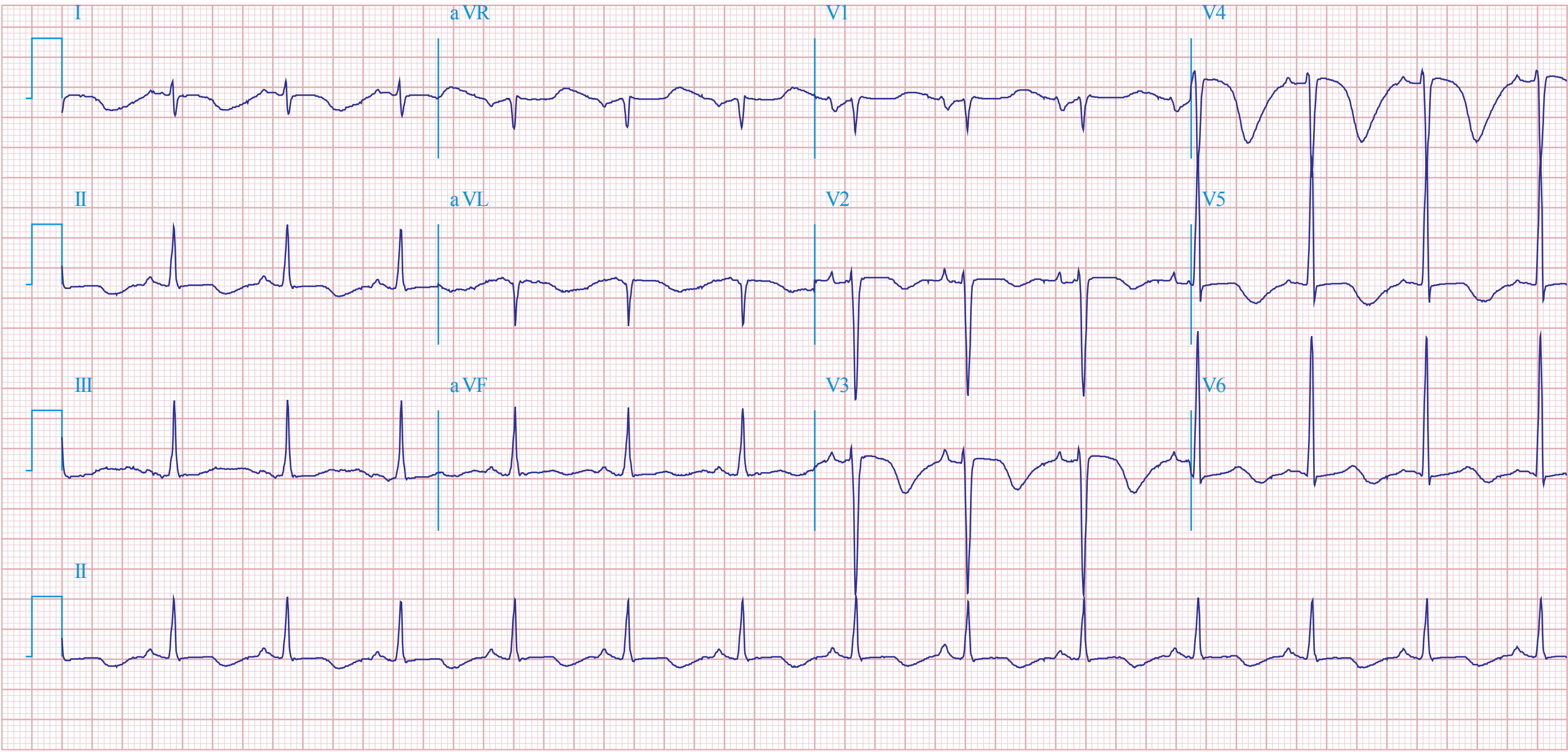


FIGURE 50-16 SR, left atrial abnormality, and LVH by voltage criteria with borderline right-axis deviation in a patient with mixed mitral stenosis (left atrial abnormality and right-axis deviation) and mitral regurgitation (LVH). Prominent precordial T-wave inversions and QT prolongation also present.

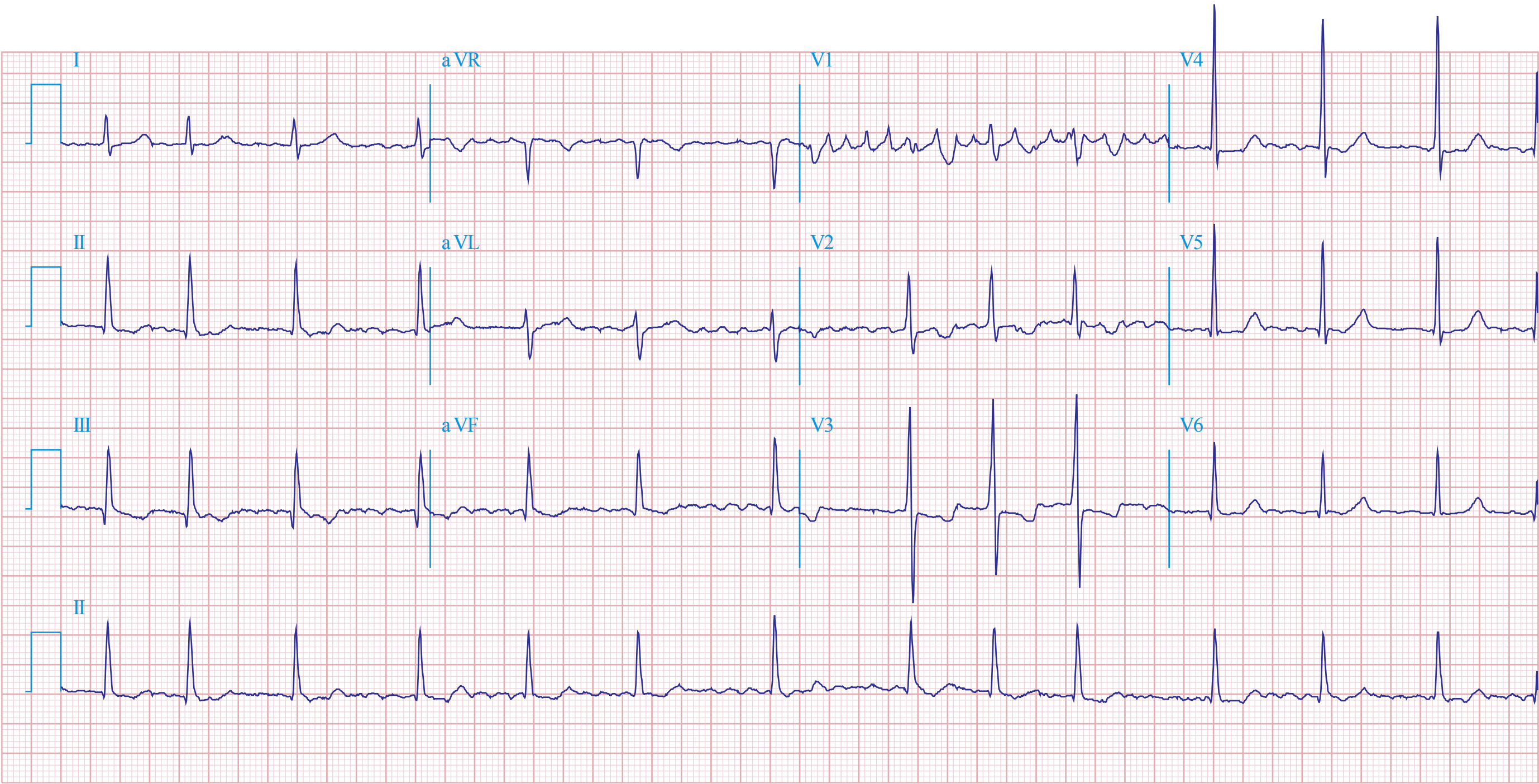


FIGURE 50-17 Coarse AF, tall R in V₂ with vertical QRS axis (positive R in aVF) indicating RVH. Tall R in V₄ may be due to concomitant LVH. Patient had severe mitral stenosis with moderate mitral regurgitation.

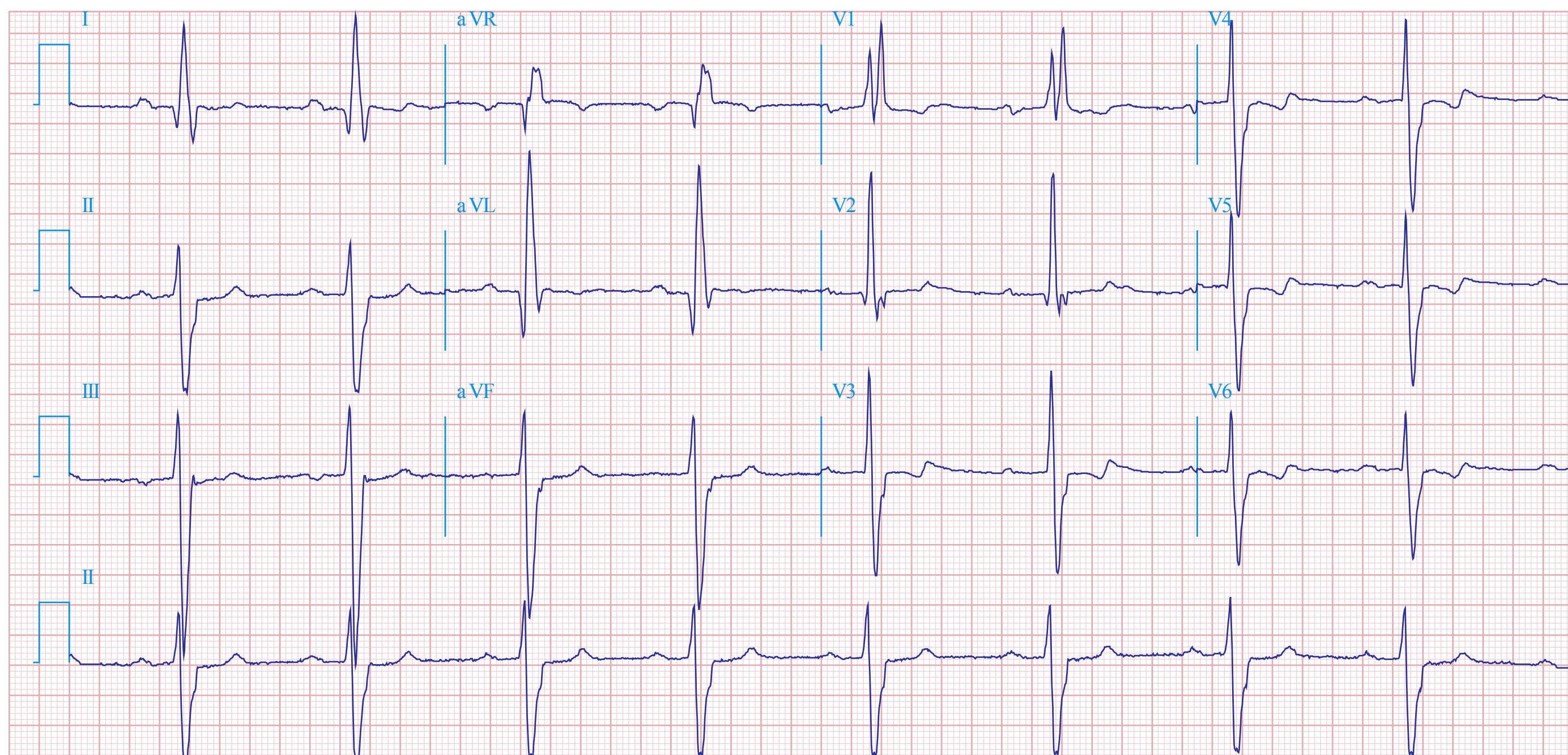


FIGURE 50-18

SR; first-degree AV “block” (PR prolongation); LVH (tall R in aVL); RBBB (wide multiphasic R wave in V1) and left

anterior fascicular block in a patient with HCM. Deep Q waves in I and aVL are consistent with septal hypertrophy.

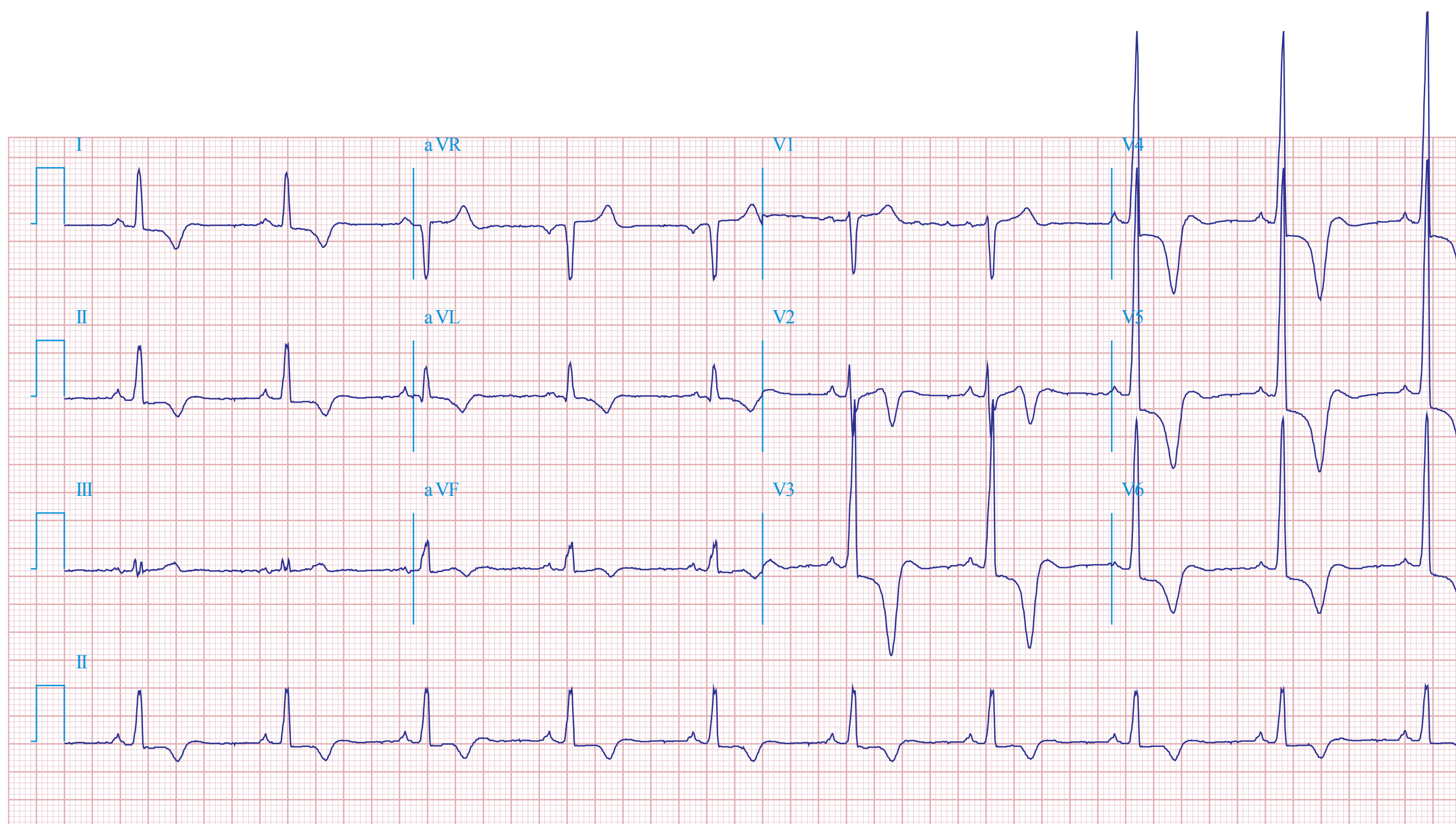


FIGURE 50-19

LVH with deep T-wave inversions in limb leads and precordial leads. Striking T-wave inversions in mid-precordial leads suggest apical HCM (Yamaguchi's syndrome).

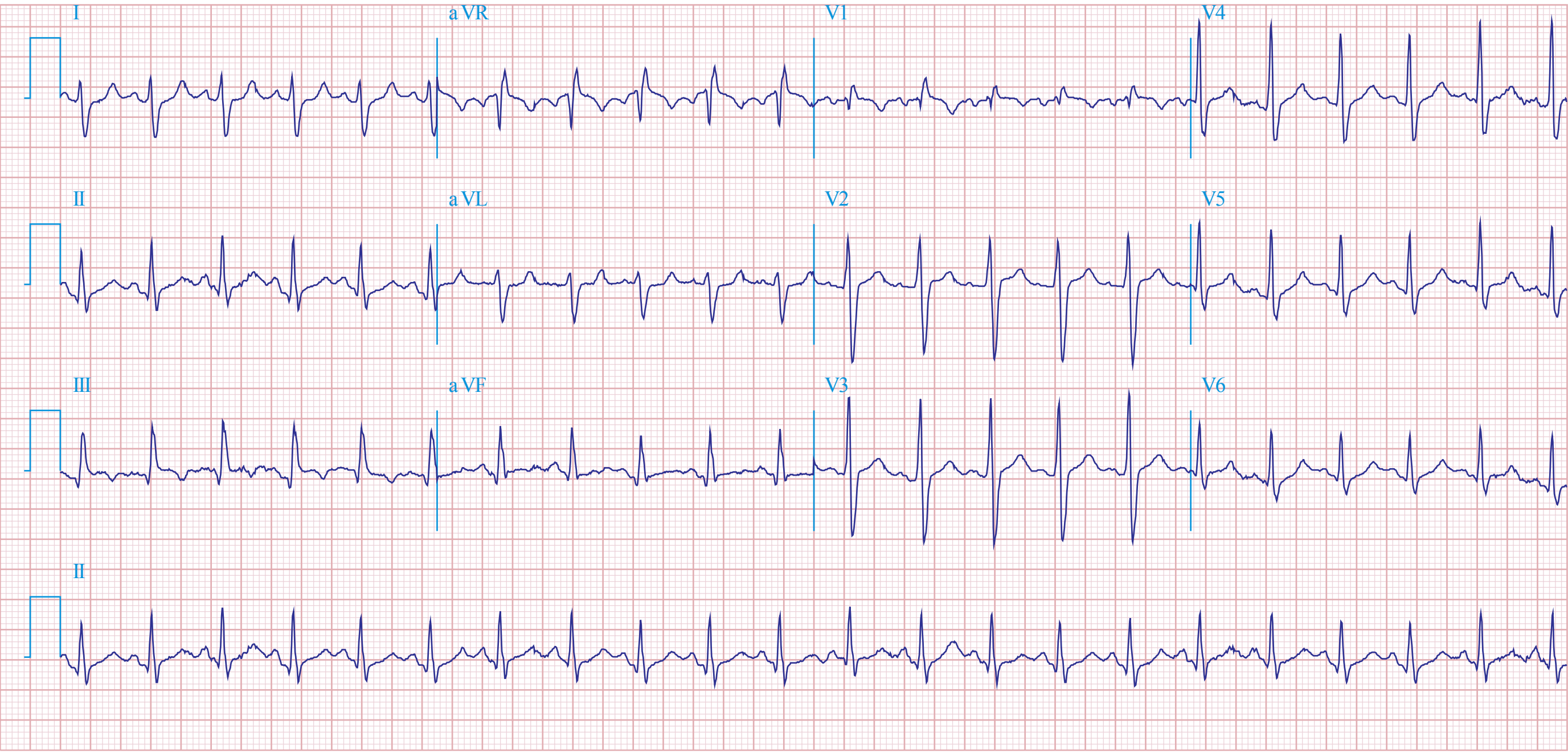


FIGURE 50-20
Sinus tachycardia with S1Q3T3 pattern (T-wave inversion in III), incomplete RBBB, and right precordial T-wave inversions consistent with acute RV overload in a patient with pulmonary emboli.

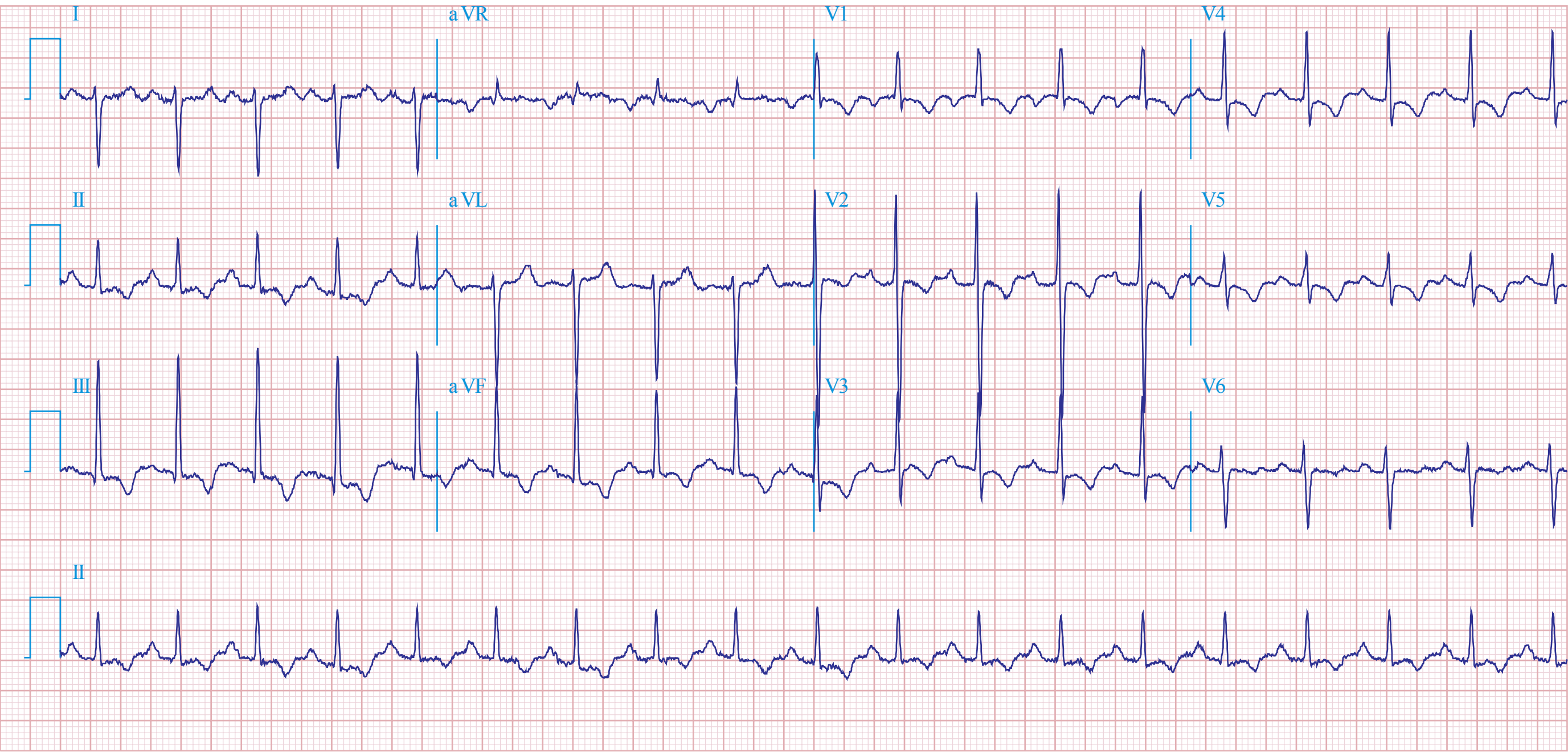


FIGURE 50-21
Sinus tachycardia, right-axis deviation, RVH with tall R in V₁ and deep S in V₆, and inverted T waves in II, III, aVF, and V₁–V₅ in a patient with atrial septal defect and severe pulmonary hypertension.

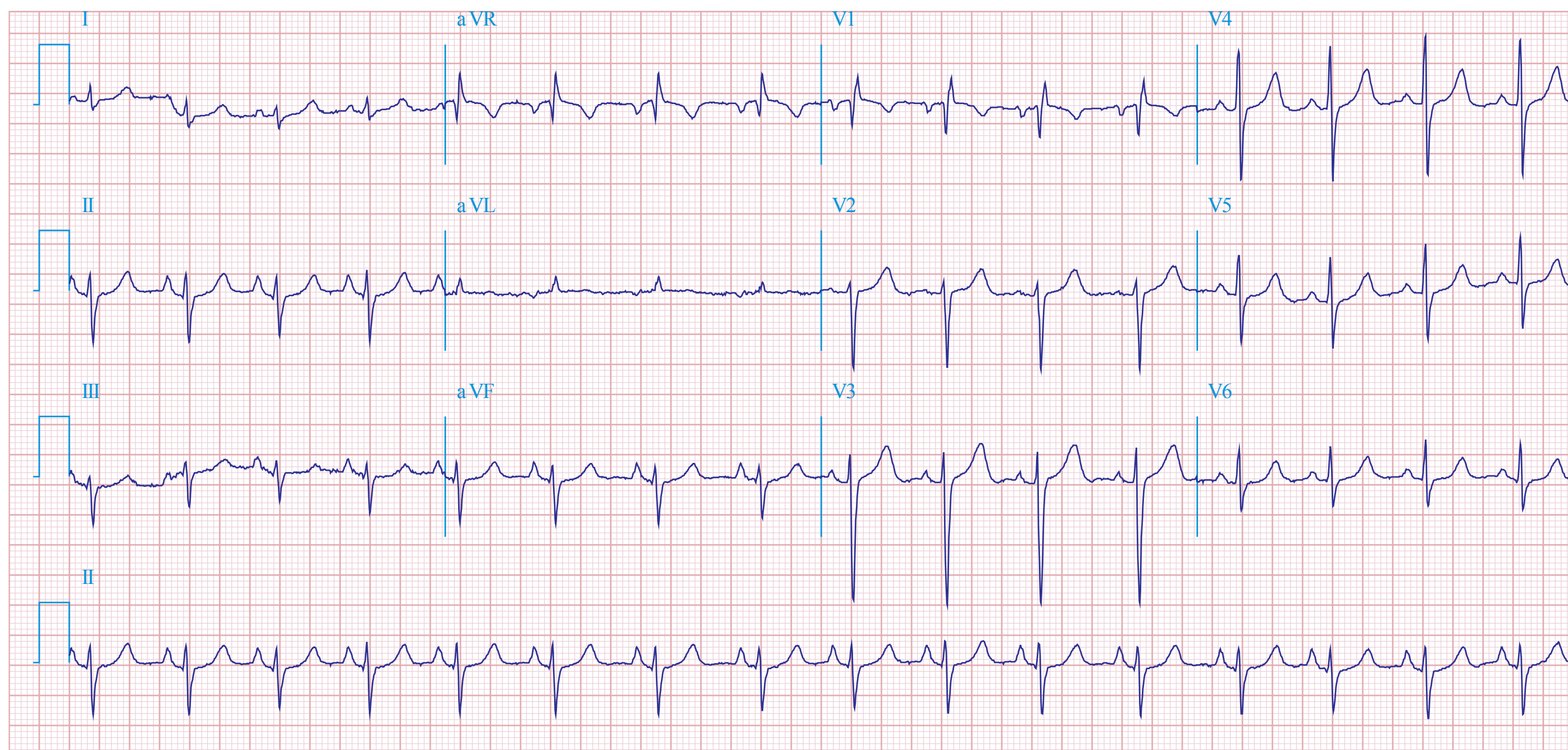


FIGURE 50-22

Signs of right atrial/RV overload in a patient with chronic obstructive lung disease: (1) peaked P waves in II; (2) QR in V_1

with narrow QRS; (3) delayed precordial transition, with terminal S waves in V_5/V_6 ; (4) superior axis deviation with an S_1 - S_2 - S_3 pattern.

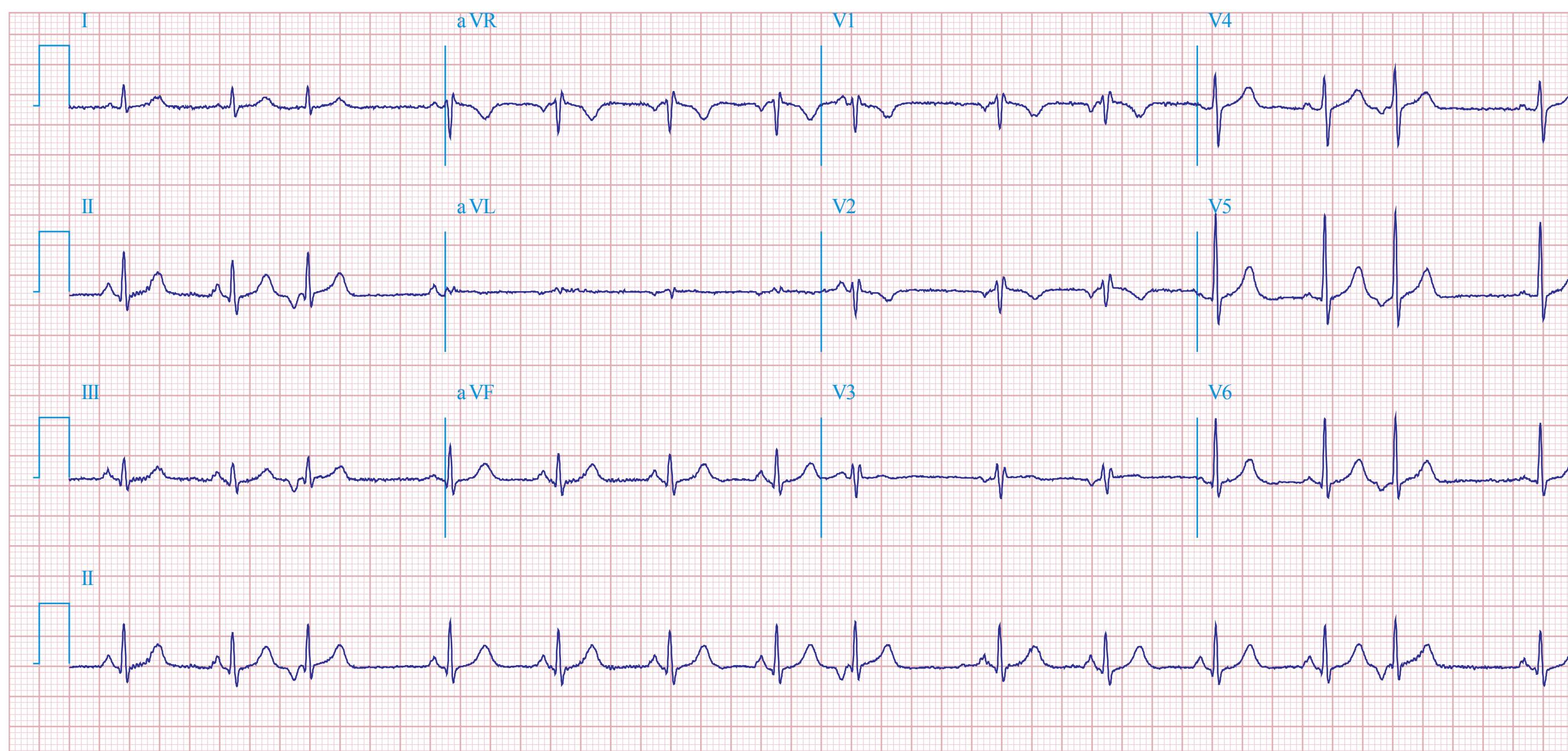


FIGURE 50-23

(1) Low voltage; (2) incomplete RBBB (rsr' in V_1 - V_3); (3) borderline peaked P waves in lead II with vertical P-wave axis (probable right atrial overload); (4) slow

R-wave progression in V_1 - V_3 ; (5) prominent S waves in V_6 ; and (6) atrial premature beats. This combination is seen typically in severe chronic obstructive lung disease.

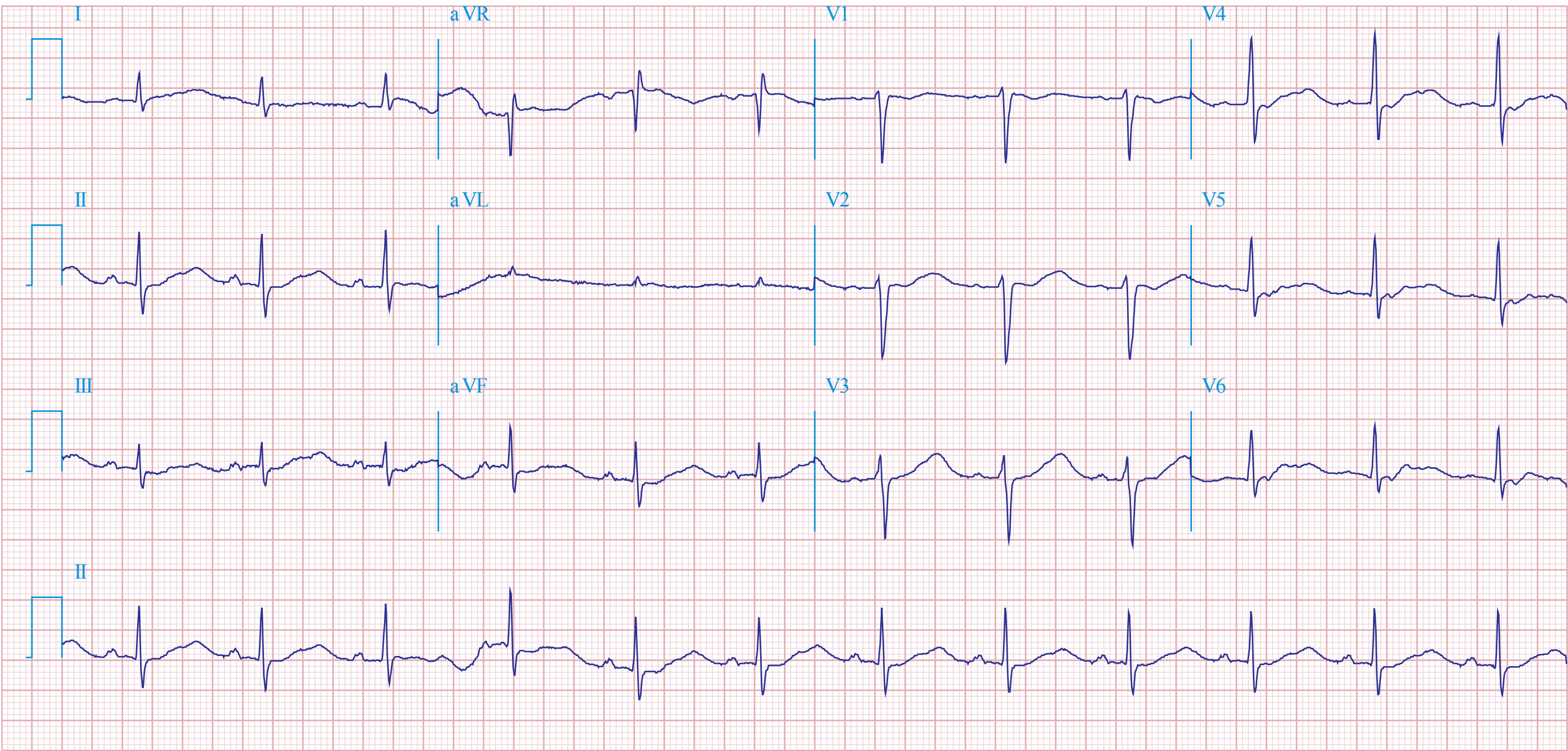


FIGURE 50-24
Prominent U waves (II, III, and V₄–V₆) with ventricular repolarization prolongation in a patient with severe hypokalemia.

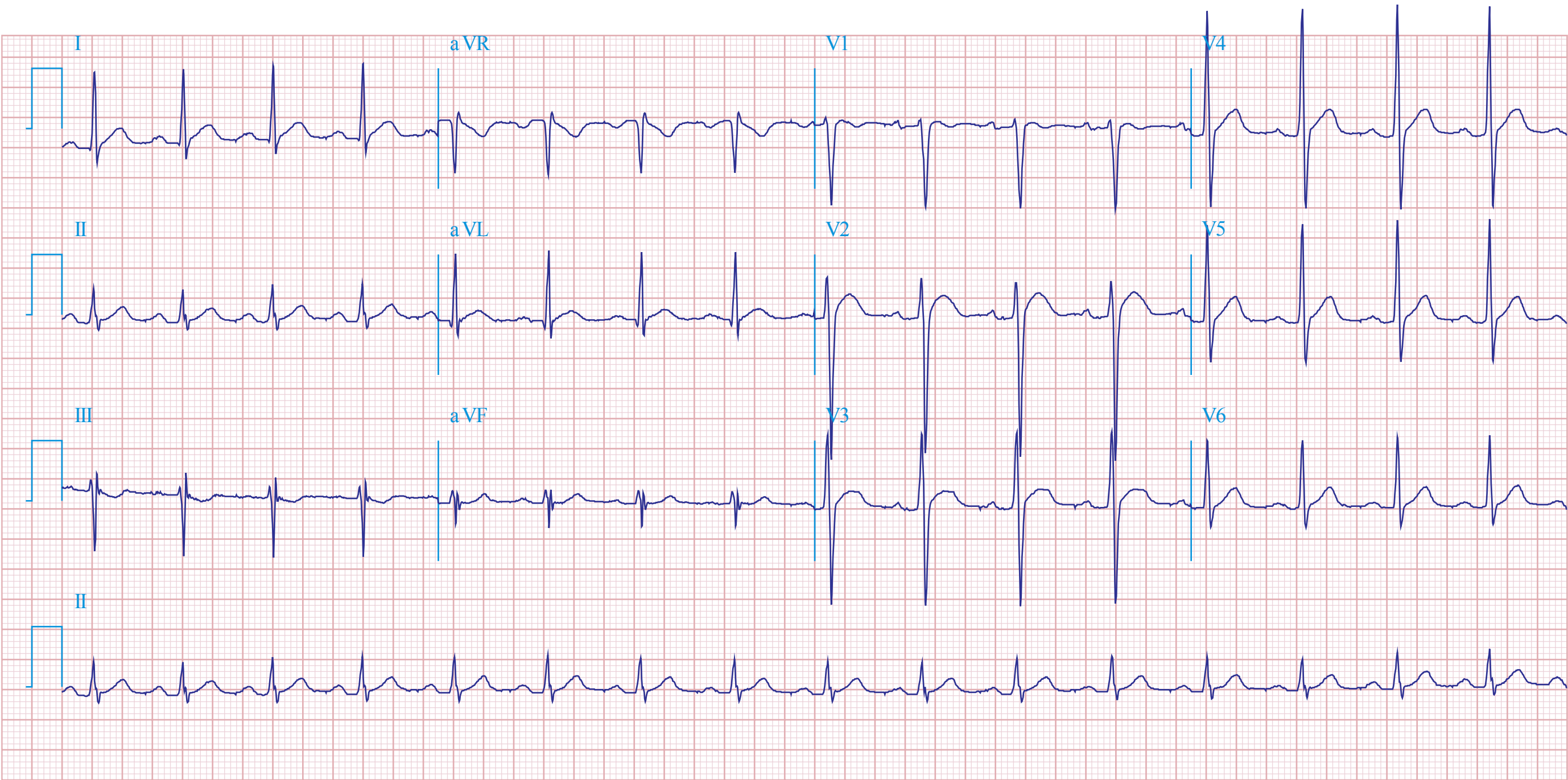


FIGURE 50-25
Abbreviated ST segment such that the T wave looks like it takes off directly from QRS in some leads (I, V₄, aVL, and V₅) in a patient with severe hypercalcemia. Note also high takeoff of ST segment in V₂/V₃ simulating acute ischemia.

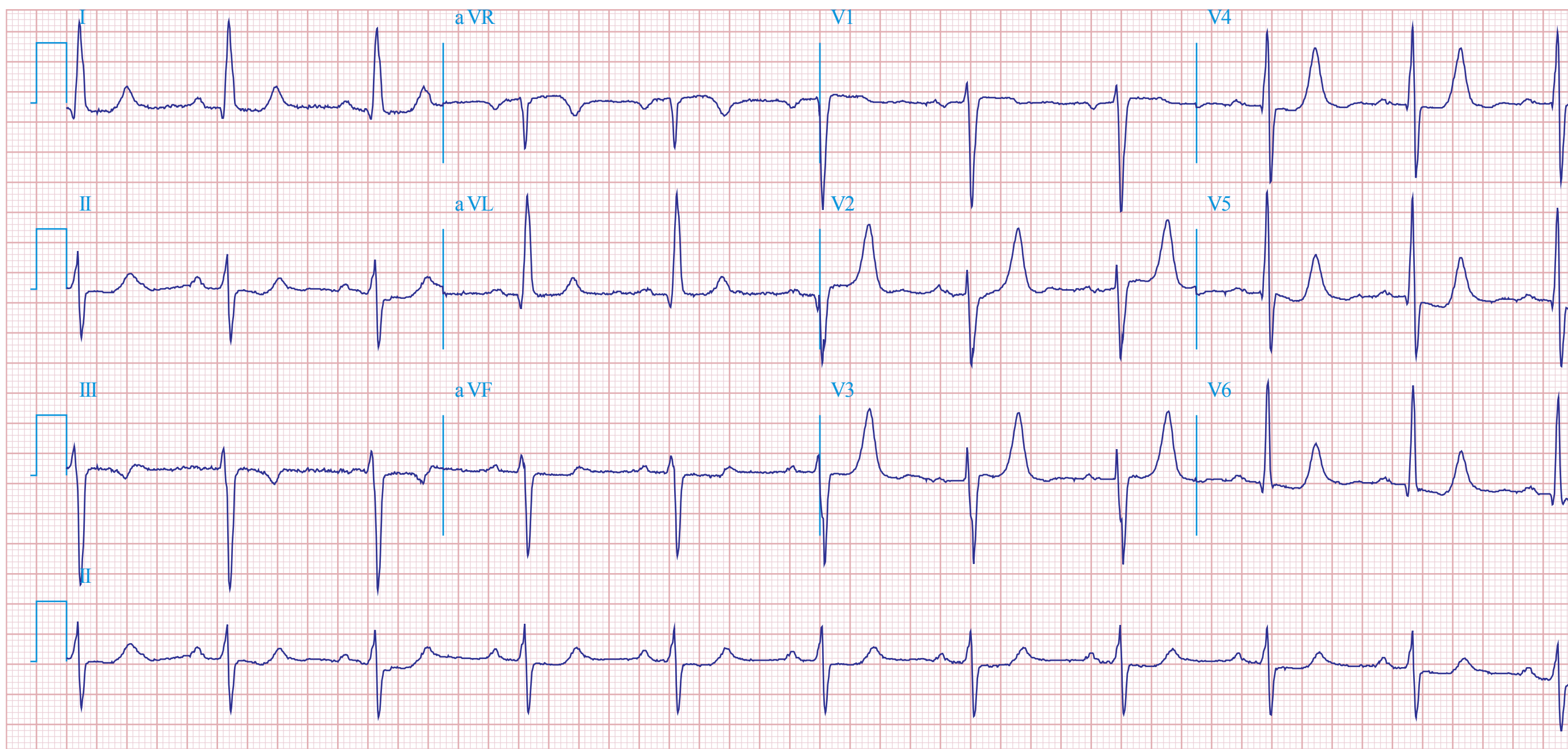


FIGURE 50-26

SR with LVH, left atrial abnormality, and tall peaked T waves in the precordial leads with inferolateral ST depressions (II, III, aVF, and V₆); left anterior fascicular block and

borderline prolonged QT interval in a patient with renal failure, hypertension, and hyperkalemia; prolonged QT is secondary to associated hypocalcemia.

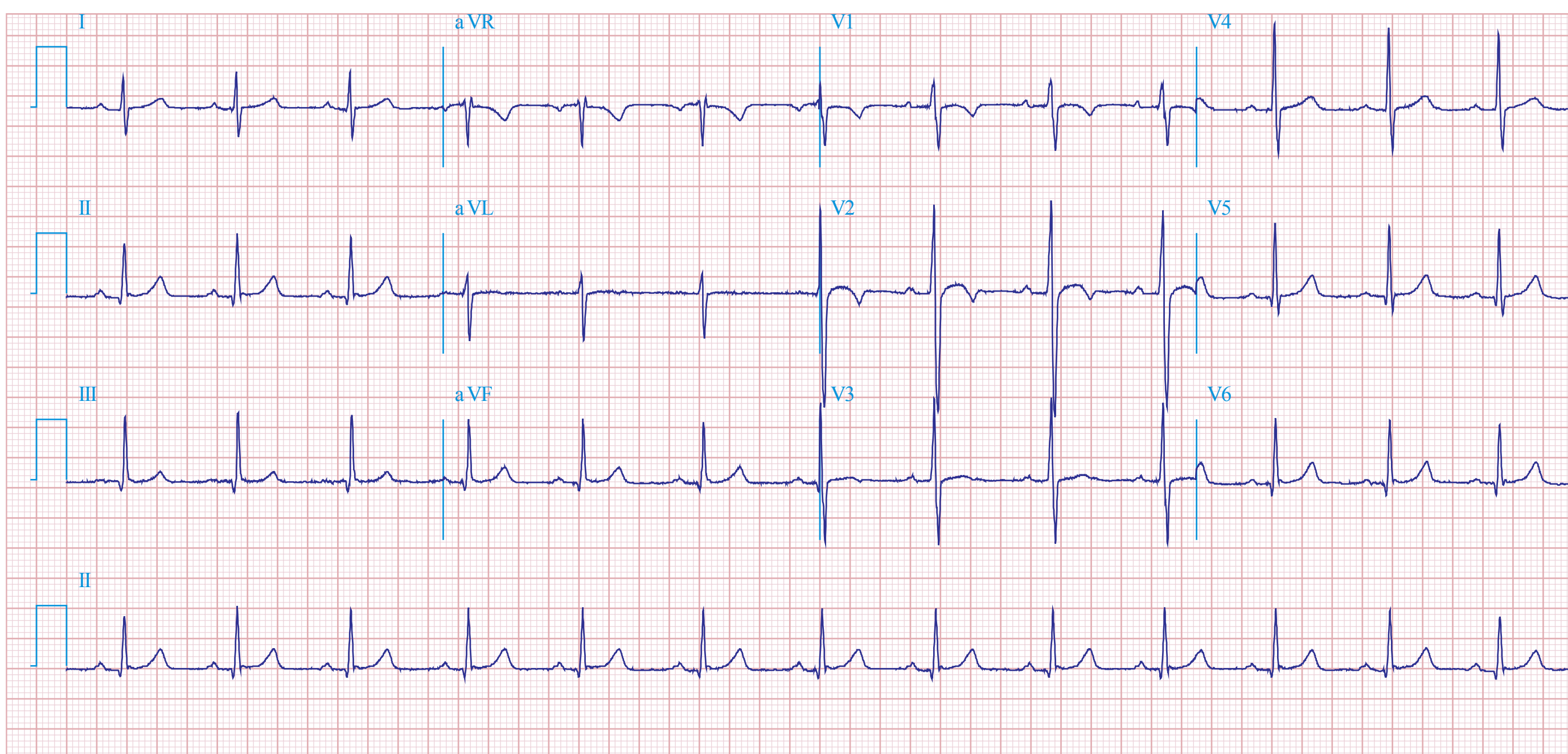


FIGURE 50-27

Normal ECG in an 11-year-old male. T-wave inversions in V₁–V₂. Vertical QRS axis (+90°) and early precordial transition between V₂ and V₃ are normal findings in children.

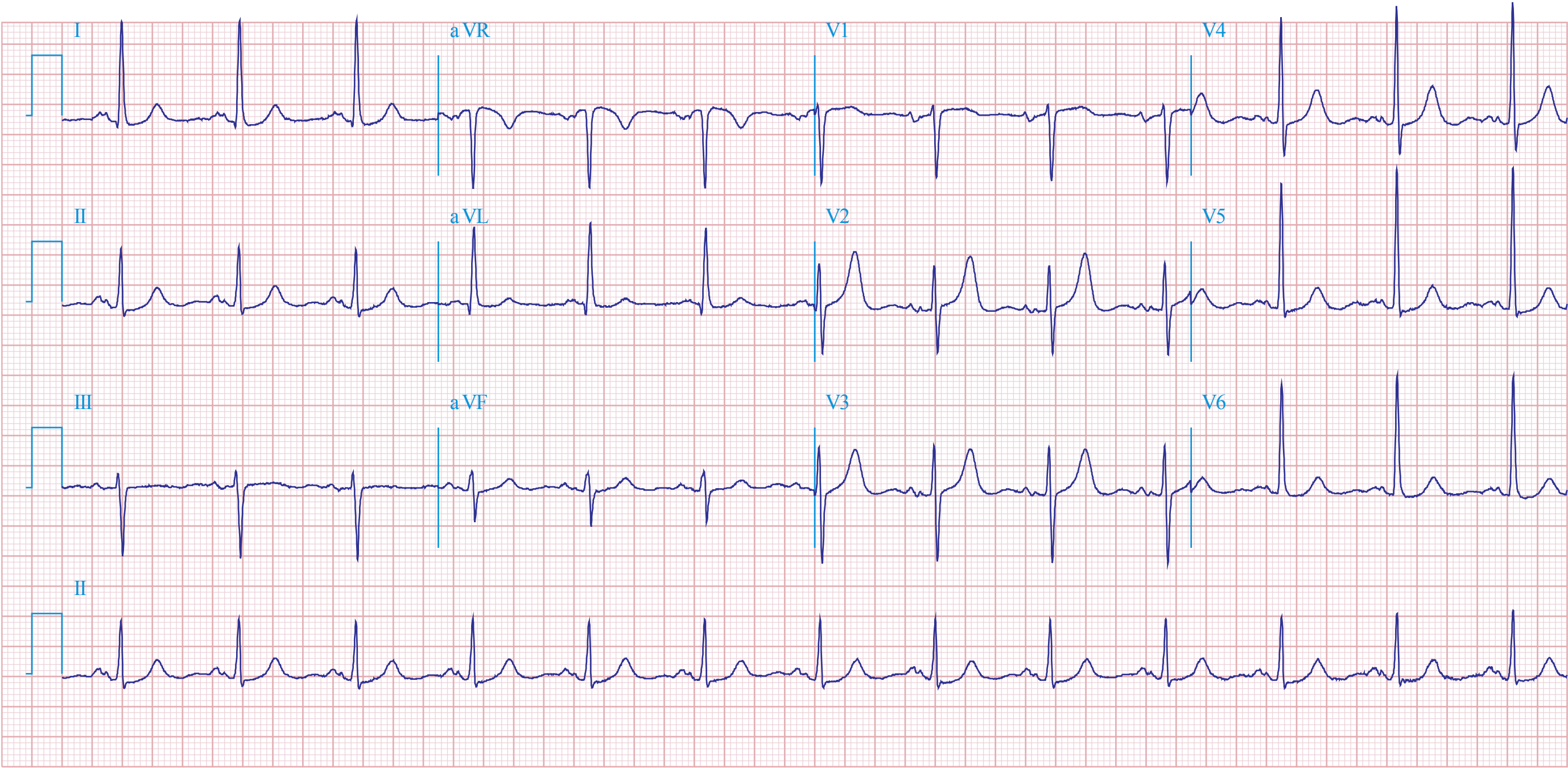


FIGURE 50-28
Left atrial abnormality and LVH in a patient with long-standing hypertension.

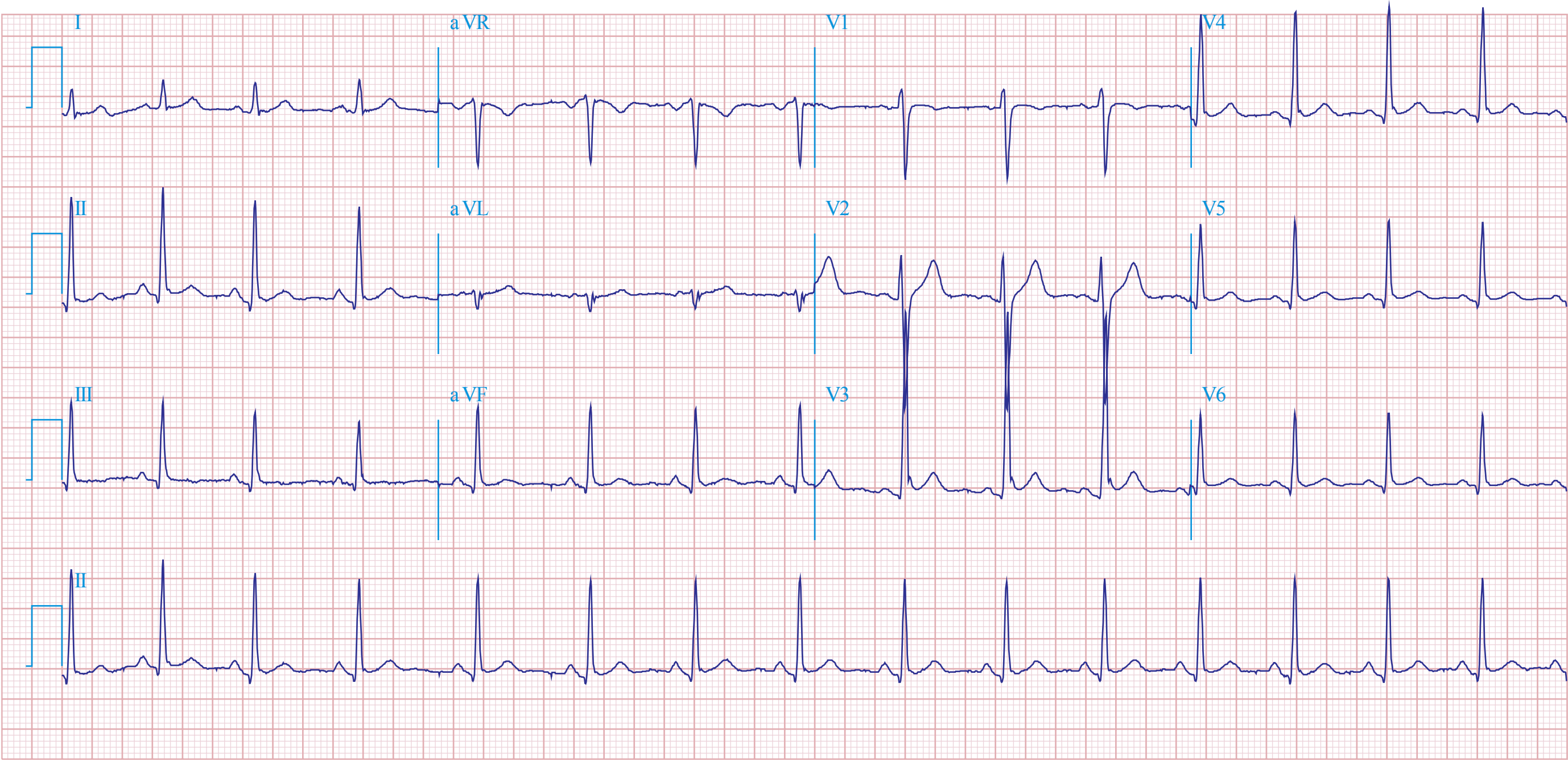


FIGURE 50-29
Normal variant ST-segment elevations in a healthy 21-year-old male (commonly referred to as benign early repolarization pattern). ST elevations exhibit upward concavity and are most apparent in V₃ and V₄, and less than 1 mm in the

limb leads. Precordial QRS voltages are prominent, but within normal limits for a young adult. No evidence of left atrial abnormality or ST depression/T-wave inversions to go along with LVH.

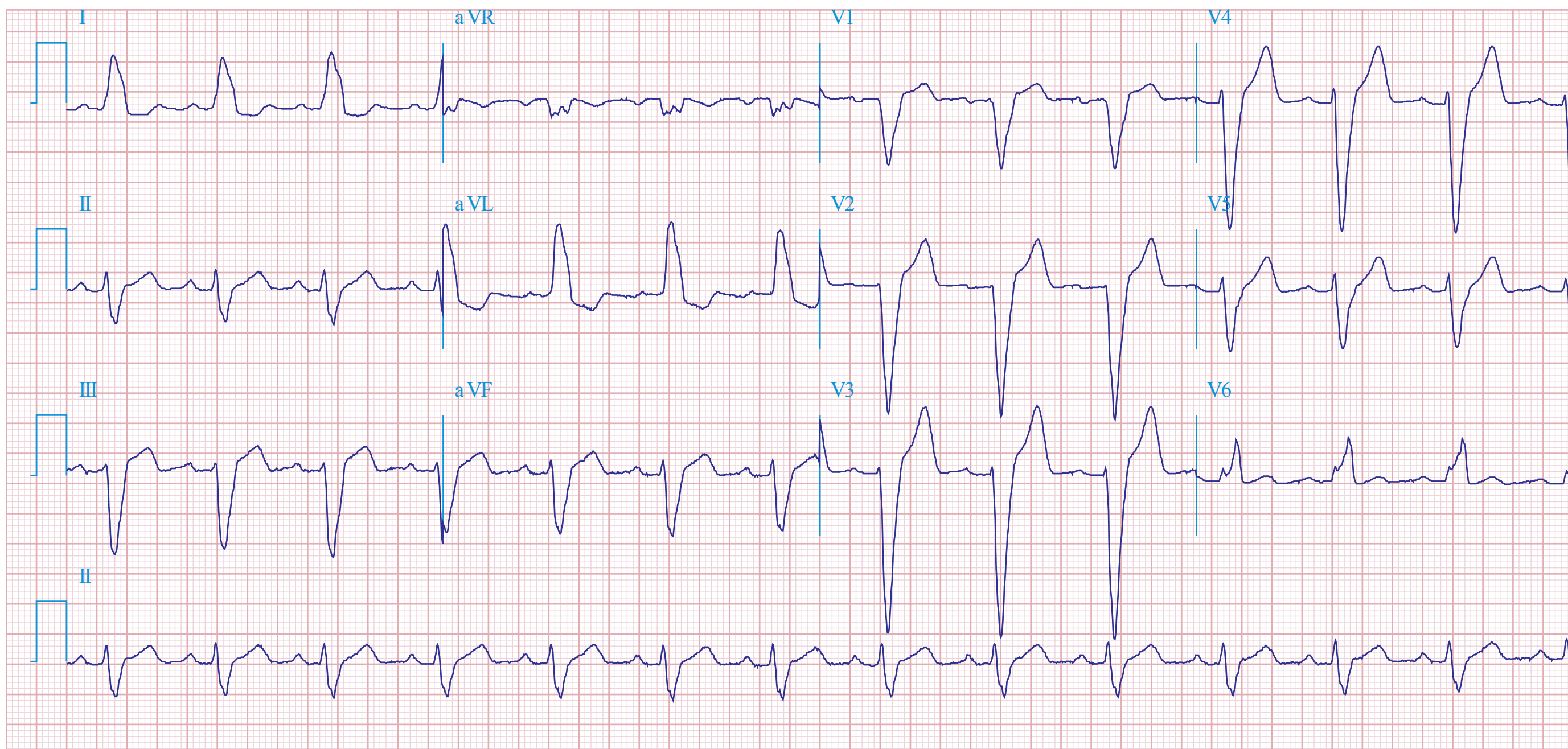


FIGURE 50-30

SR with **first-degree** AV“block” (PR interval = 0.24 s) and complete LBBB.

MISCELLANEOUS

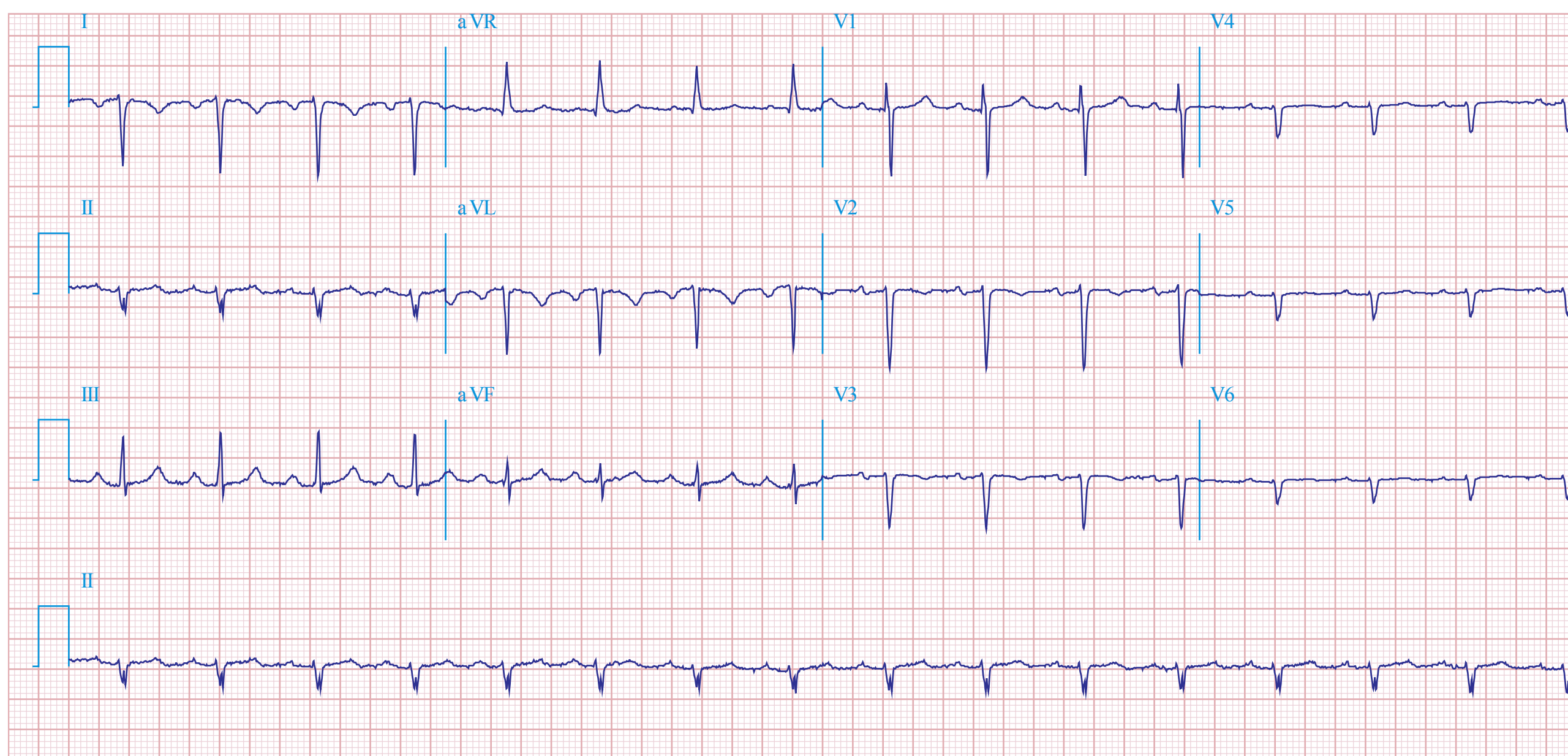


FIGURE 50-31

Dextrocardia with: (1) inverted P waves in I and aVL; (2) negative QRS complex and T wave in I; and (3) progressively decreasing voltage across the precordium.

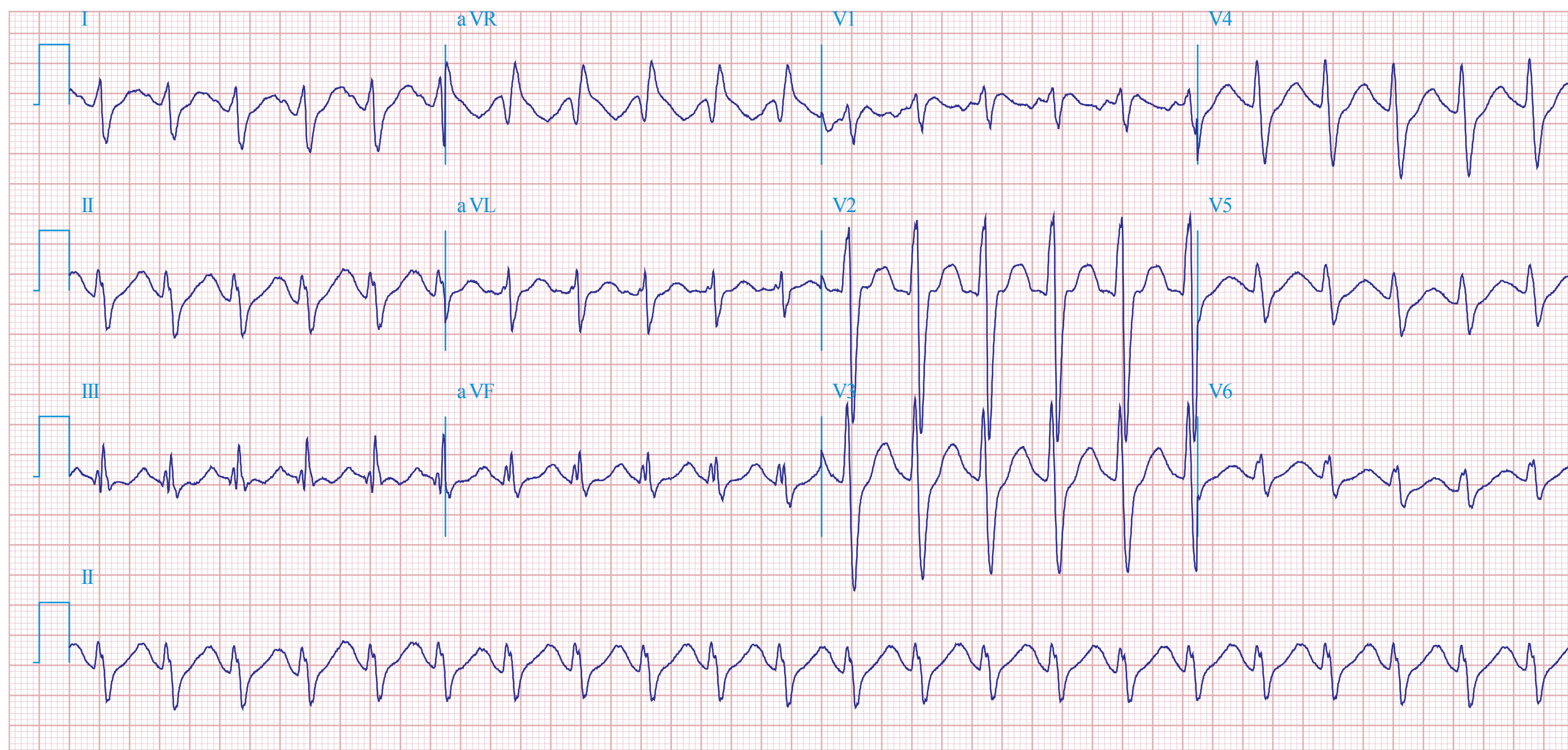


FIGURE 50-32

Sinus tachycardia; intraventricular conduction delay (IVCD) with a rightward QRS axis. QT interval is prolonged for the rate. The triad of sinus tachycardia, a wide QRS complex, and

a long QT in appropriate clinical context suggests tricyclic antidepressant overdose. Terminal S wave (rS) in I and terminal R wave (qR) in aVR are also noted as part of this IVCD variant.

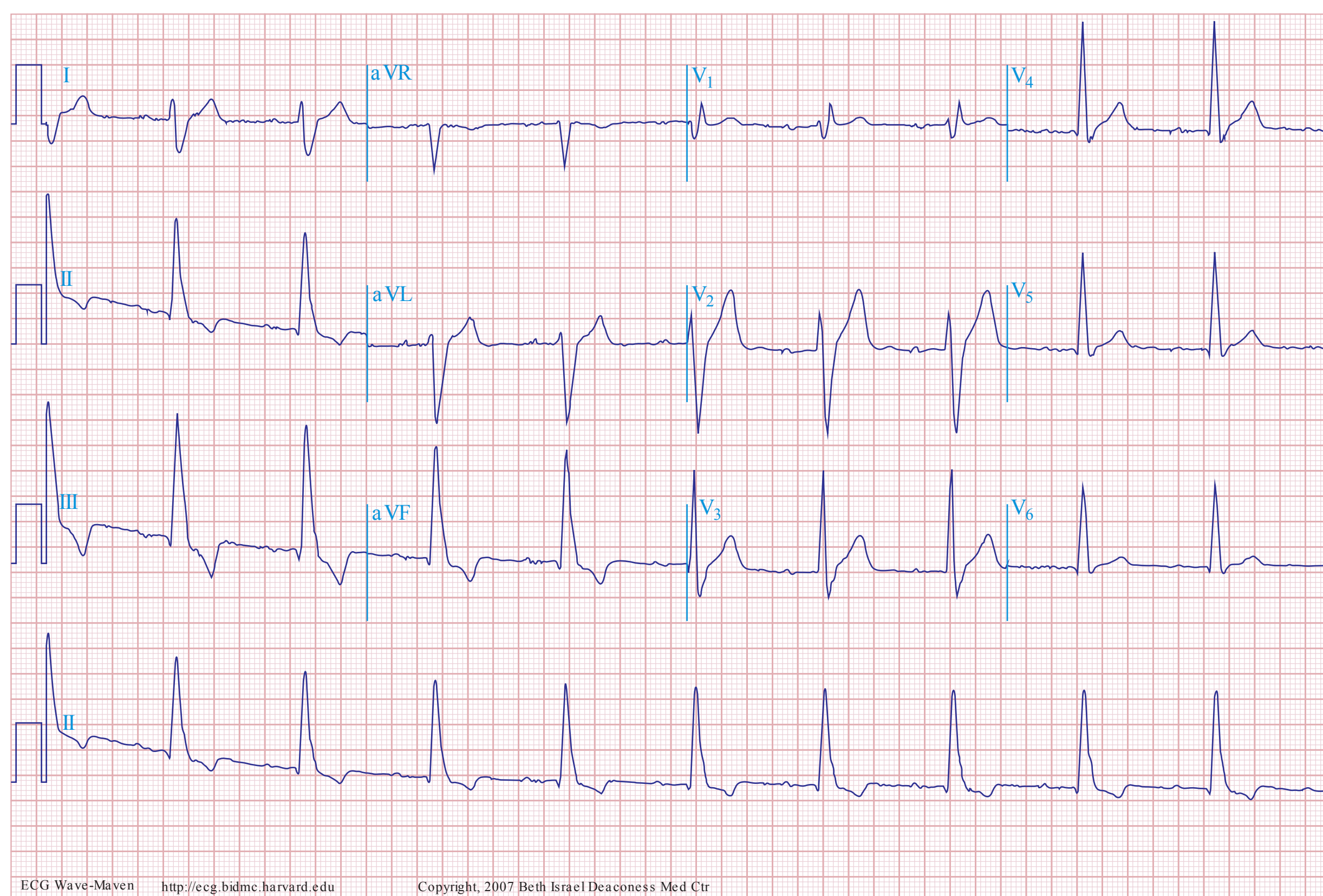


FIGURE 50-33

Borderline sinus bradycardia (59 beats/min), prolonged PR interval (250 ms), and RBBB are present with marked right-axis deviation (RAD), the latter consistent with left posterior fascicular block (LPFB). LPFB is a diagnosis of exclusion, which requires ruling out lead reversal, normal

variant, RV overload syndromes, or lateral MI, in particular, as causes of the RAD. This ECG also shows nondiagnostic Q waves in the inferior leads. In concert with RBBB, the LPFB indicates bifascicular block. (From LA Nathanson et al: ECG Wave-Maven. <http://ecg.bidmc.harvard.edu>.)

CHAPTER 51

ATLAS OF NONINVASIVE IMAGING



Marcelo F. Di Carli ■ Raymond Y. Kwong ■ Scott D. Solomon

This chapter provides “movie” image clips as they are viewed in clinical practice, as well as additional static images. Noninvasive cardiac imaging is essential to the diagnosis and management of patients with known or suspected cardiovascular disease. This atlas supplements **Chap. 12**, which describes the principles and clinical applications of these important techniques.

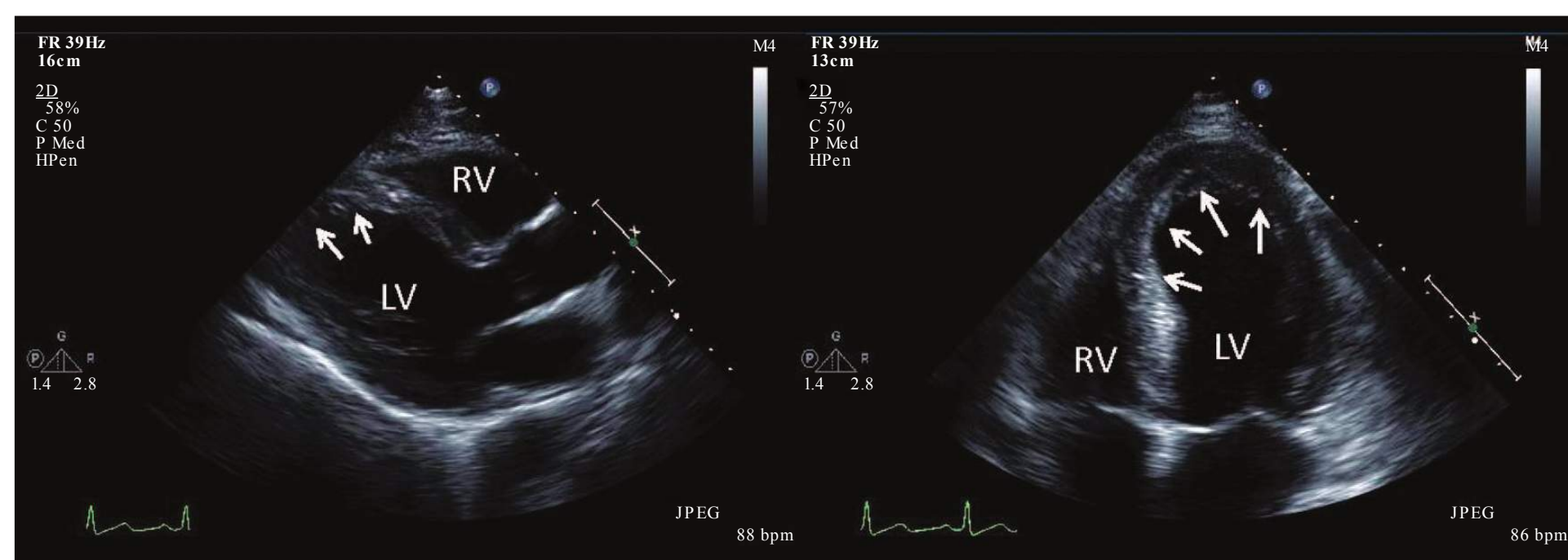


FIGURE 51-1

A 48-year-old man with new-onset substernal chest pain. Echocardiography shows evidence of acute anterior myocardial infarction involving the interventricular septum and apex secondary to an occlusion of the left anterior descending coronary

artery seen from the parasternal long axis view (left) and the apical four-chamber view (right). LV, left ventricle; RV, right ventricle. (See Videos 51-1 and 51-2.)

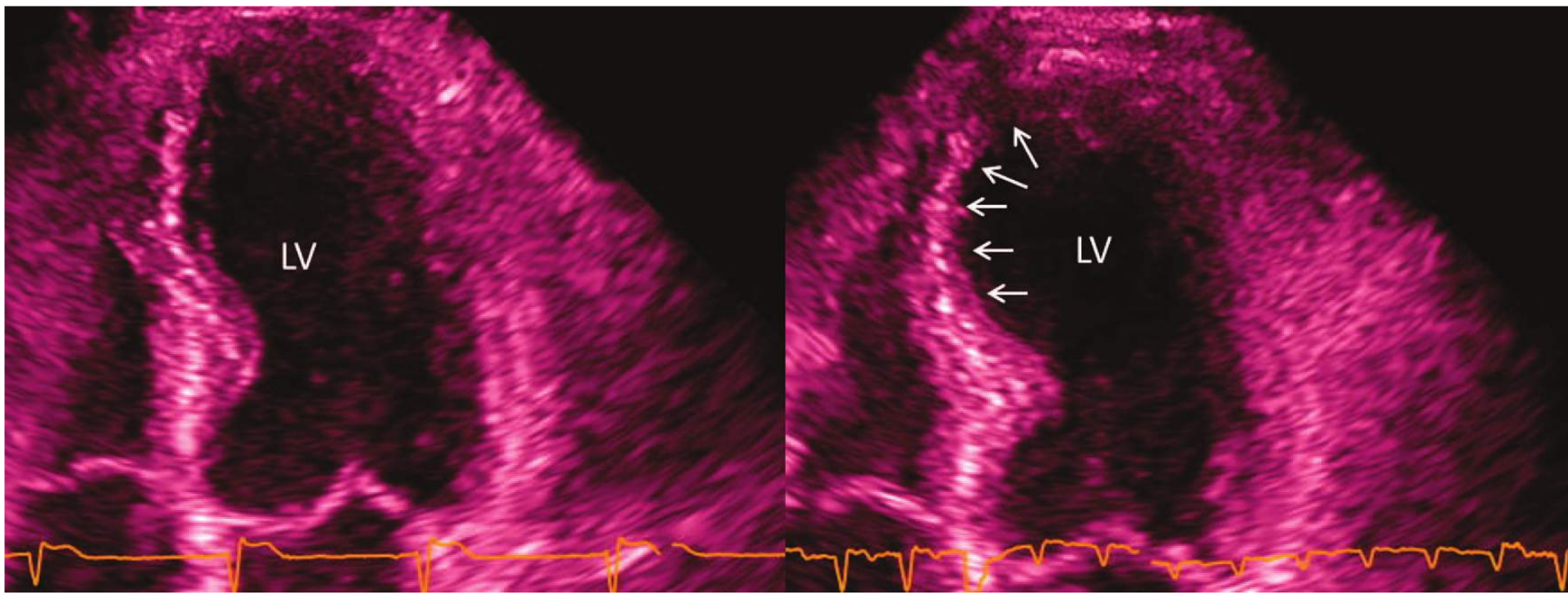


FIGURE 51-2

A 55-year-old man with exertional chest discomfort and dyspnea. He exercised for 12 min on a standard Bruce protocol, experiencing typical chest pain and ST-segment depression in V₂–V₅. End-systolic frame of a stress echocardiogram shows apical four-chamber view at rest (left) and after exercise (right). After

exercise, there is a clear regional wall motion abnormality in the distal septum through the apex, consistent with a stenosis in the left anterior descending artery distribution (arrows). LV, left ventricle. (See Videos 51-3 and 51-4.)

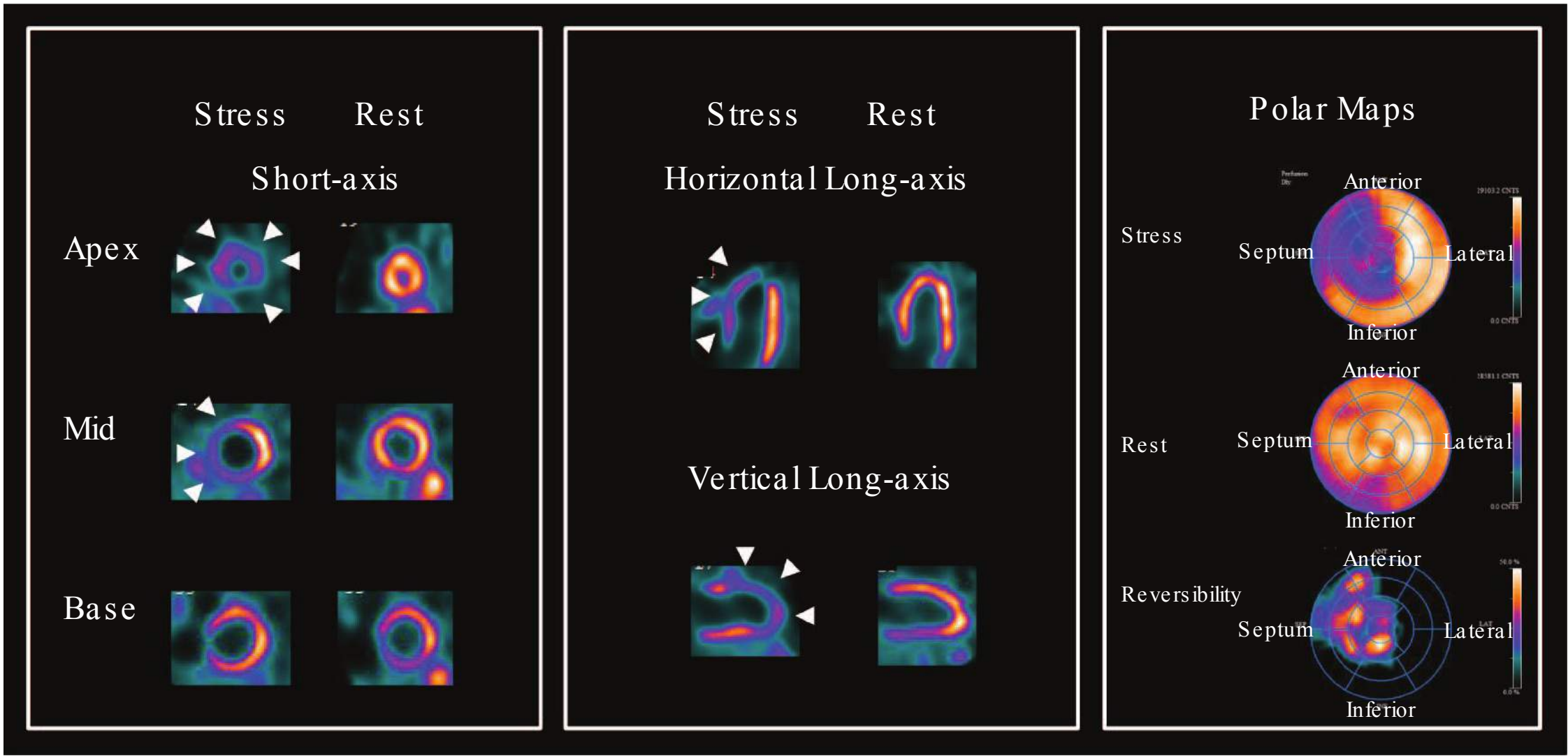


FIGURE 51-3

Exercise single-photon emission computed tomography (SPECT) myocardial perfusion technetium-99m (^{99m}Tc) sestamibi scan in a 54-year-old male with a history of coronary artery disease and a prior coronary stent. The stress images (left and middle) show a large defect involving the apex, all apical segments, mid-inferior, mid-inferoseptum, and mid-anteroseptum

(arrowheads), which is completely reversible at rest (right), reflecting a large area of exercise-induced myocardial ischemia throughout the left anterior descending coronary territory. The bull's eye displays on the right panel depict the semiquantitative extent of ischemia (light yellow and blue areas represent the extent and severity of ischemia).

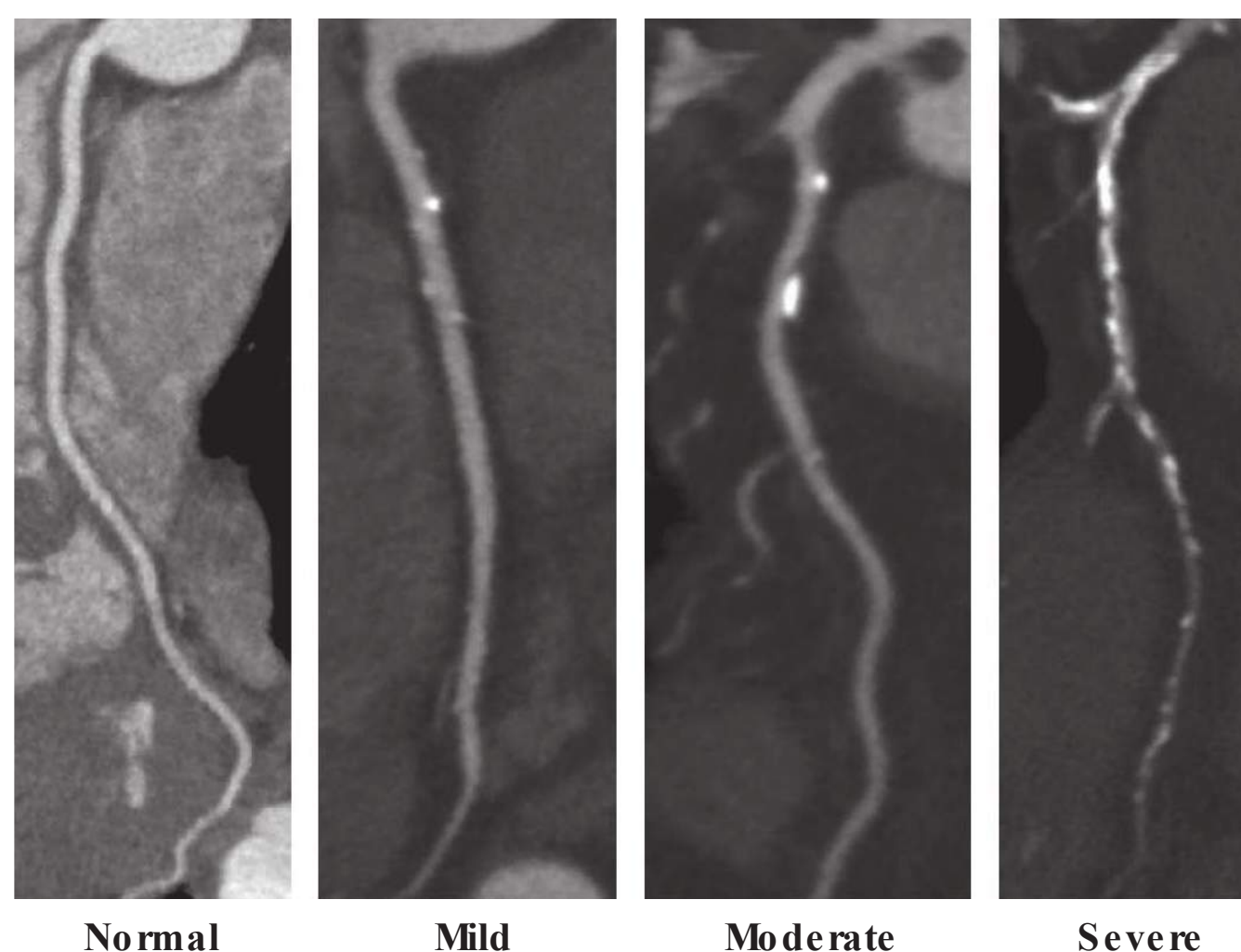
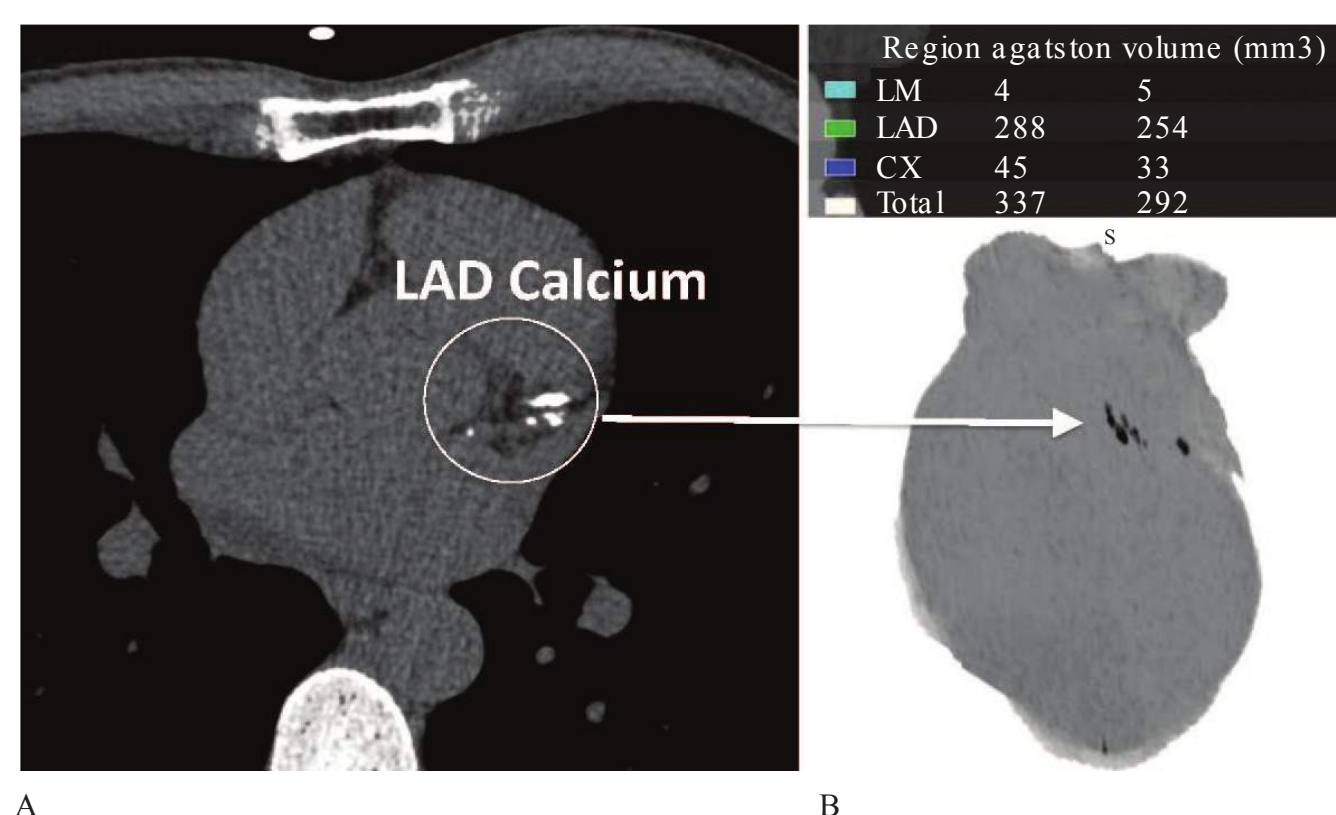


FIGURE 51-4

Coronary computed tomography angiography (CTA) Curved multiplanar reformations demonstrating coronary artery disease severity, defined as normal (no plaque or stenosis), mild (<40%), moderate (40–69%), and severe (>70%) luminal narrowing. By guidelines for CTA reporting, alternative classification

provides for stenosis grading as normal, minimal (1–24%), mild (25–49%), moderate (50–69%), severe (70–99%), and occluded (100%). (From GL Raff et al: SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 3:122, 2009; with permission.)



- CAC score 271e = 96th percentile for age, race and ethnicity¹
- 10-year hard CHD risk is 6% (observed age) vs 30% (arterial age)^{2#}

FIGURE 51-5

Coronary artery calcium (CAC) scan on a 51-year-old white male without clinical cardiovascular disease or treated diabetes, referred for CAC for risk stratification to guide preventive therapies. A. Gated, noncontrast cardiac computed tomography (CT; 3-mm slice thickness), axial view, demonstrating calcified left anterior descending (LAD) artery atherosclerosis. B. Whole-heart three-dimensional image reconstruction, inverted maximum-intensity projection, demonstrating overall burden of CAC with predominant LAD distribution (arrow). Top right. CAC scores for

each coronary artery with calcified plaque involvement, scored by Agatston method and total volume. #For white male with observed age 51 years, total cholesterol 220 mg/dL, high-density lipoprotein 45 mg/dL, nonsmoker, no hypertension, and systolic blood pressure 120 mmHg. Calculated arterial age is 81 years. CHD, coronary heart disease; CX, left circumflex artery; LM, left main artery. ¹Data from RLMcClelland et al: Circulation 113:30-37, 2006. ²Data from RLMcClelland et al: Am J Cardiol 103:59-63, 2009.

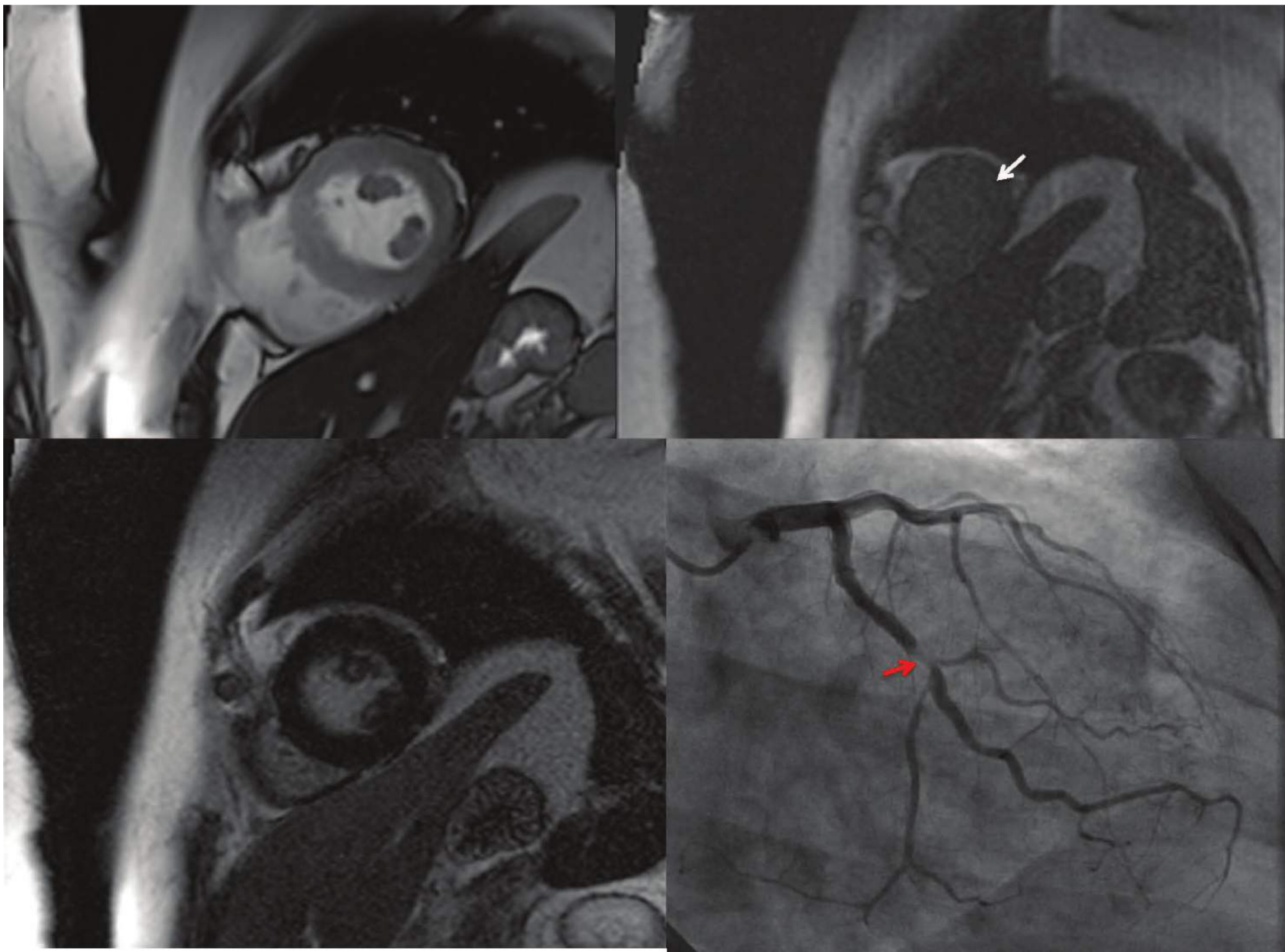


FIGURE 51-6

Cardiac magnetic resonance (CMR) stress myocardial perfusion images in a 60-year-old patient with atypical chest pain. Cine movie short-axis image (left upper panel) shows normal left ventricle size and global and regional function at rest. During vasodilator stress, there is marked reduction of lateral wall perfusion (white arrow, right upper panel) as well as a mild defect in the septal wall. This region is confirmed to be viable by matching

late gadolinium enhancement imaging (left lower panel), which demonstrated no evidence of infarction in the lateral wall. These findings are consistent with a severe coronary stenosis in the left circumflex artery. On angiography performed subsequently, there is a tight lesion in the left circumflex artery (red arrow, right lower panel). (See Videos 51-5 and 51-6.)

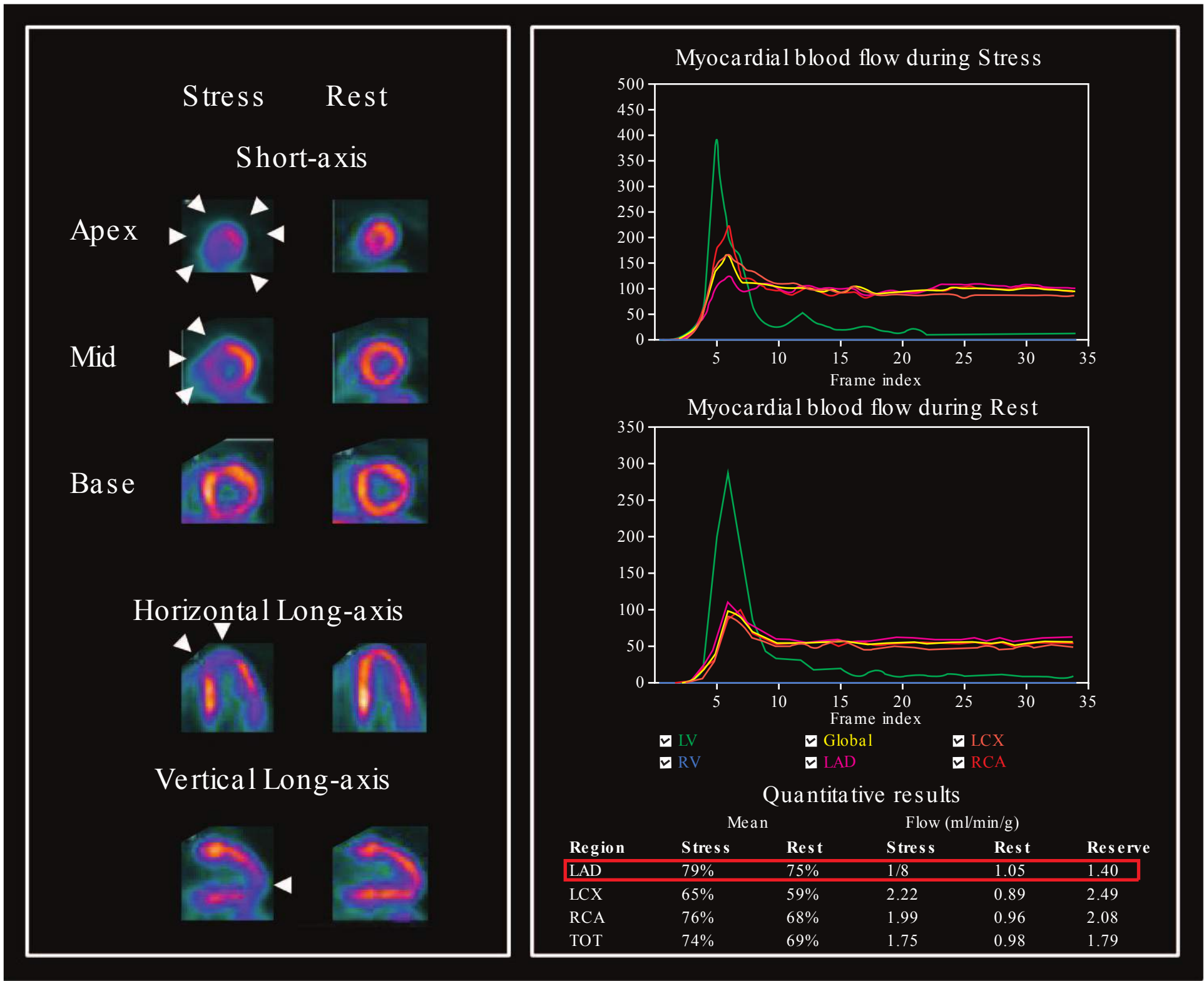


FIGURE 51-7

Adenosine positron emission tomography (PET) myocardial perfusion ¹³N-ammonia scan in a 60-year-old female with atypical chest pain. The stress images (left) show a large defect involving the apex, all apical segments, mid-inferior, mid-inferoseptum, and mid-anteroseptum (arrowheads), which is completely reversible at rest (right). This is consistent with a medium-sized area of stress-induced ischemia in the mid portion of the left anterior descending (LAD) coronary artery. The right panel illustrates the time-activity curves used for quantification of myocardial blood flow (in mL/min per g of tissue) at peak stress (upper panel) and at rest (lower panel). Coronary flow reserve is then calculated as the ratio of stress/rest myocardial blood flow. The coronary flow reserve is abnormal in the LAD territory, and normal in the left circumflex (LCX) and right coronary artery (RCA) territories (i.e., >2.0). TOT, total left ventricle.

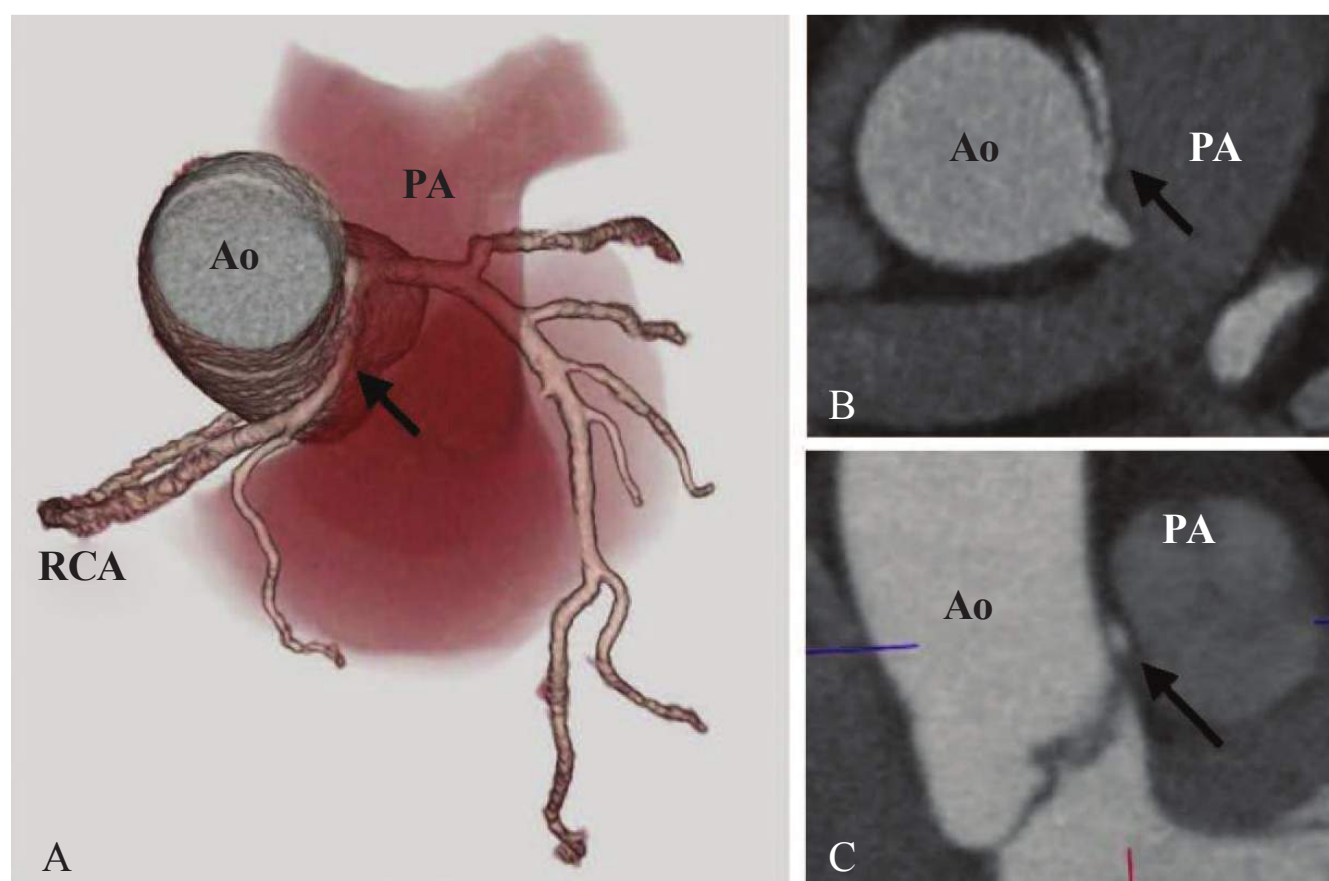


FIGURE 51-8

Coronary computed tomography angiography (CTA) obtained on a 35-year-old female presenting to an outpatient clinic with a history of unexplained syncope and a 6-month complaint of intermittent, atypical chest pain occurring primarily during rest. Physical examination is normal. An exercise treadmill test is performed demonstrating good exercise capacity with no exertional chest pain or ischemic ECG changes. For persistent, unexplained symptoms, coronary CTA is obtained. A. Three-dimensional cardiac CT image reconstruction demonstrating anomalous right coronary artery (RCA) origin from the left coronary cusp with an acute angle takeoff (arrow) and an intraarterial course between the aorta (Ao) and main pulmonary artery (PA). B, C. Contrast-enhanced CTA in two-dimensional axial (B) and coronal oblique views (C) demonstrating proximal RCA intraarterial course between the Ao and main PA.

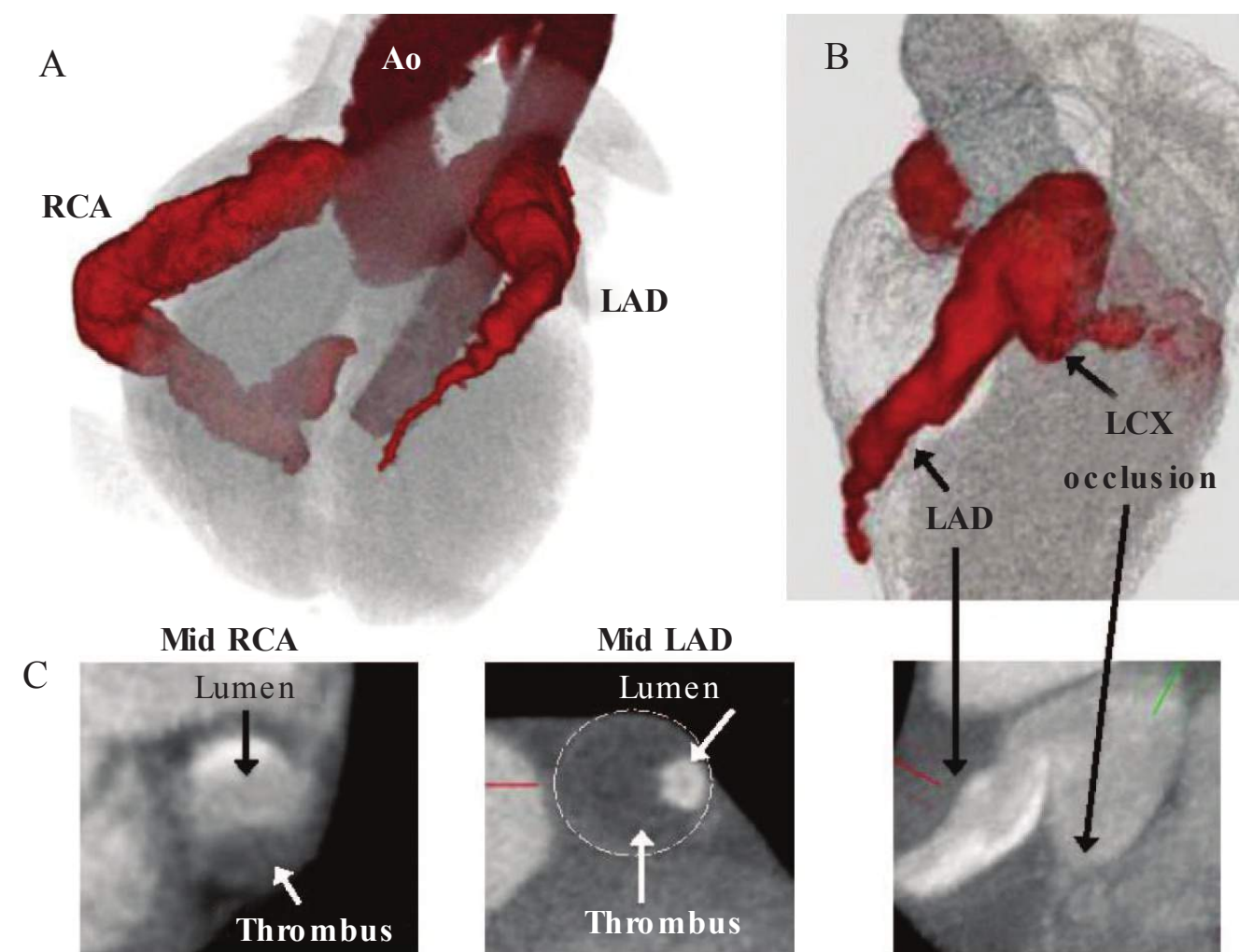


FIGURE 51-9

Coronary computed tomography angiography (CTA) obtained from a 13-year-old boy with a history of Kawasaki disease who presented with limited exercise capacity and occasional, atypical chest pain. A, B. Three-dimensional cardiac CT image reconstruction demonstrating large three-vessel coronary artery diffuse aneurysms with proximal, nondominant left circumflex (LCX) artery occlusion. C. Two-dimensional contrast-enhanced coronary CTA demonstrating mid-RCA and mid-LAD thrombi that are nonocclusive layered and near circumferential thrombi, respectively, and proximal LCX occlusion. Ao, aorta; CT, computed tomography; LAD, left anterior descending; RCA, right coronary artery.

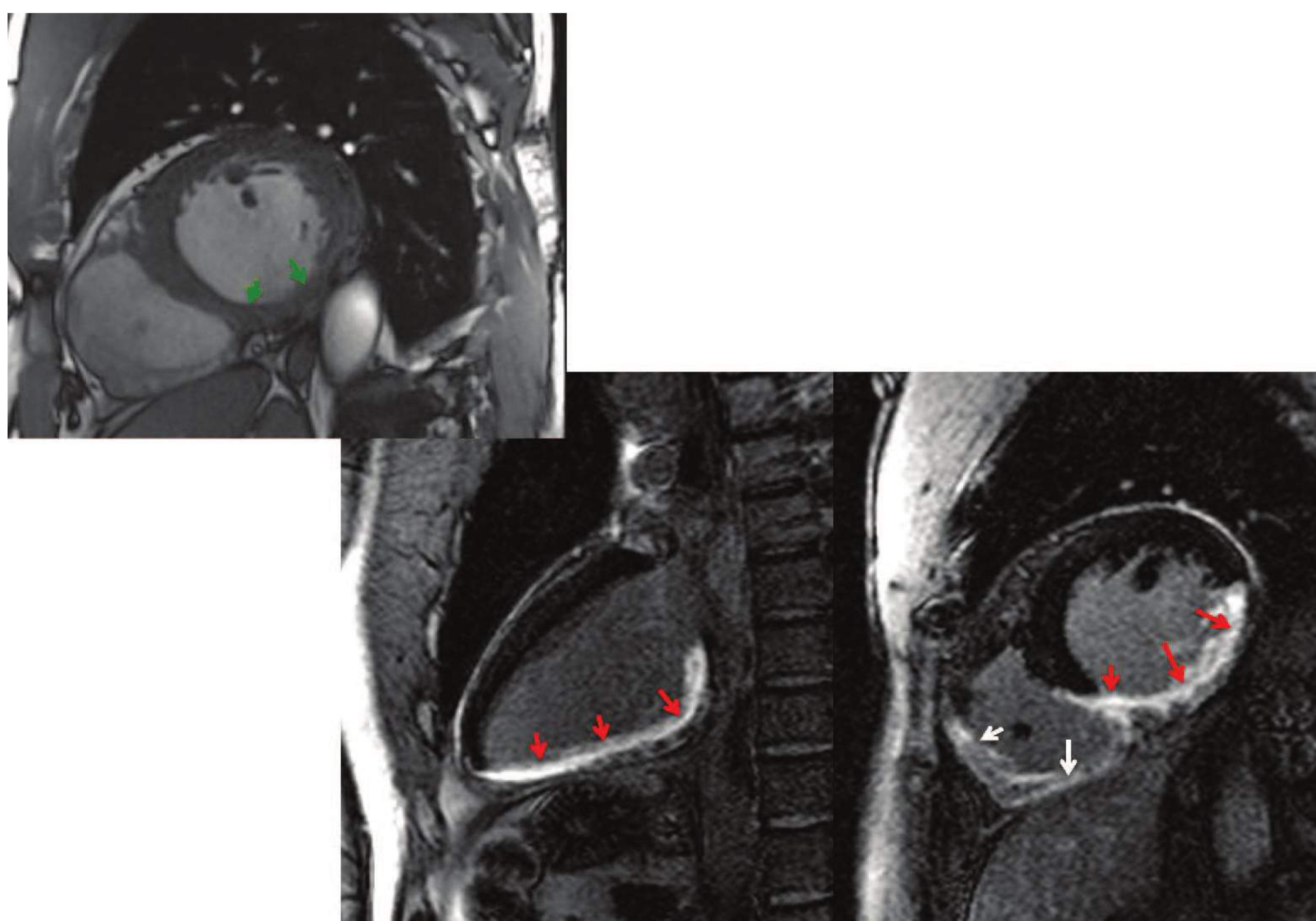


FIGURE 51-10

A case of viability assessment in a patient with inferior myocardial infarction. The cine movie in the upper panel shows an area of inferior akinesis (green arrows). Magnetic resonance image demonstrates transmurular contrast enhancement of the inferior wall (red arrows) and the right ventricle (white arrows), which is consistent with infarction. Imaging the heart 10–15 min after injection of gadolinium allows for the accumulation of gadolinium in infarcted tissue (red arrows), which identifies nonviable infarcted myocardium as bright. Viability assessment, as in this case, can provide guidance for any benefits of invasive coronary intervention. In this case, the inferior wall is nonviable. Apart from the inferior wall infarction (red arrows), there is extensive right ventricular infarction (white arrows). (See Video 51-7.)

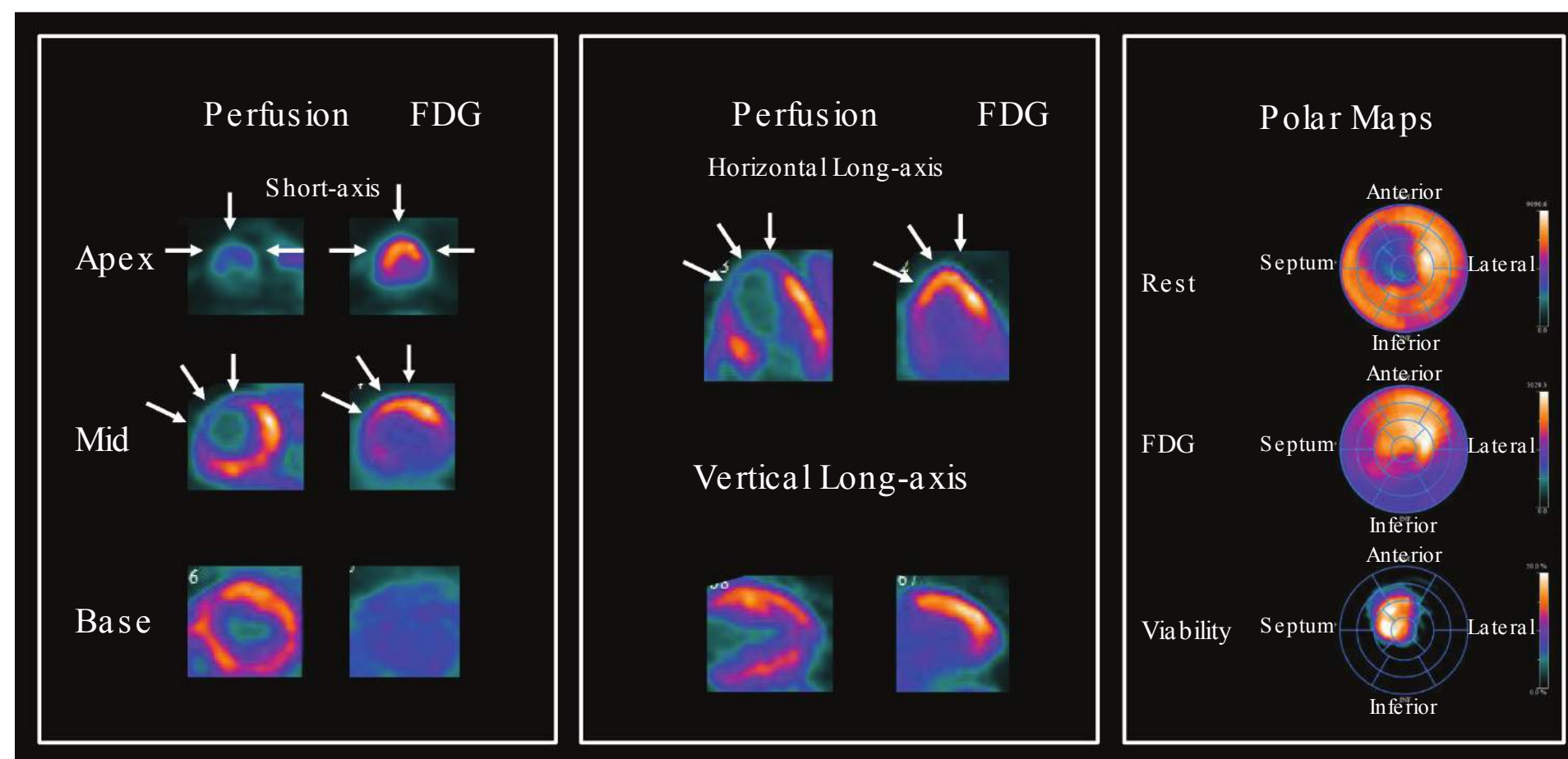


FIGURE 51-11

Rest myocardial perfusion and metabolism positron emission tomography (PET) scan obtained with ^{13}N -ammonia (perfusion) and ^{18}F -fluorodeoxyglucose (FDG; glucose metabolism) in a 48-year-old male with a prior myocardial infarction. The rest perfusion images show a large defect involving the apex,

apical segments, and mid-anteroseptal and anterior segments (arrowheads), which has associated increase in glucose uptake (perfusion-metabolic mismatch), reflecting viable but hibernating myocardium throughout the left anterior descending coronary territory.

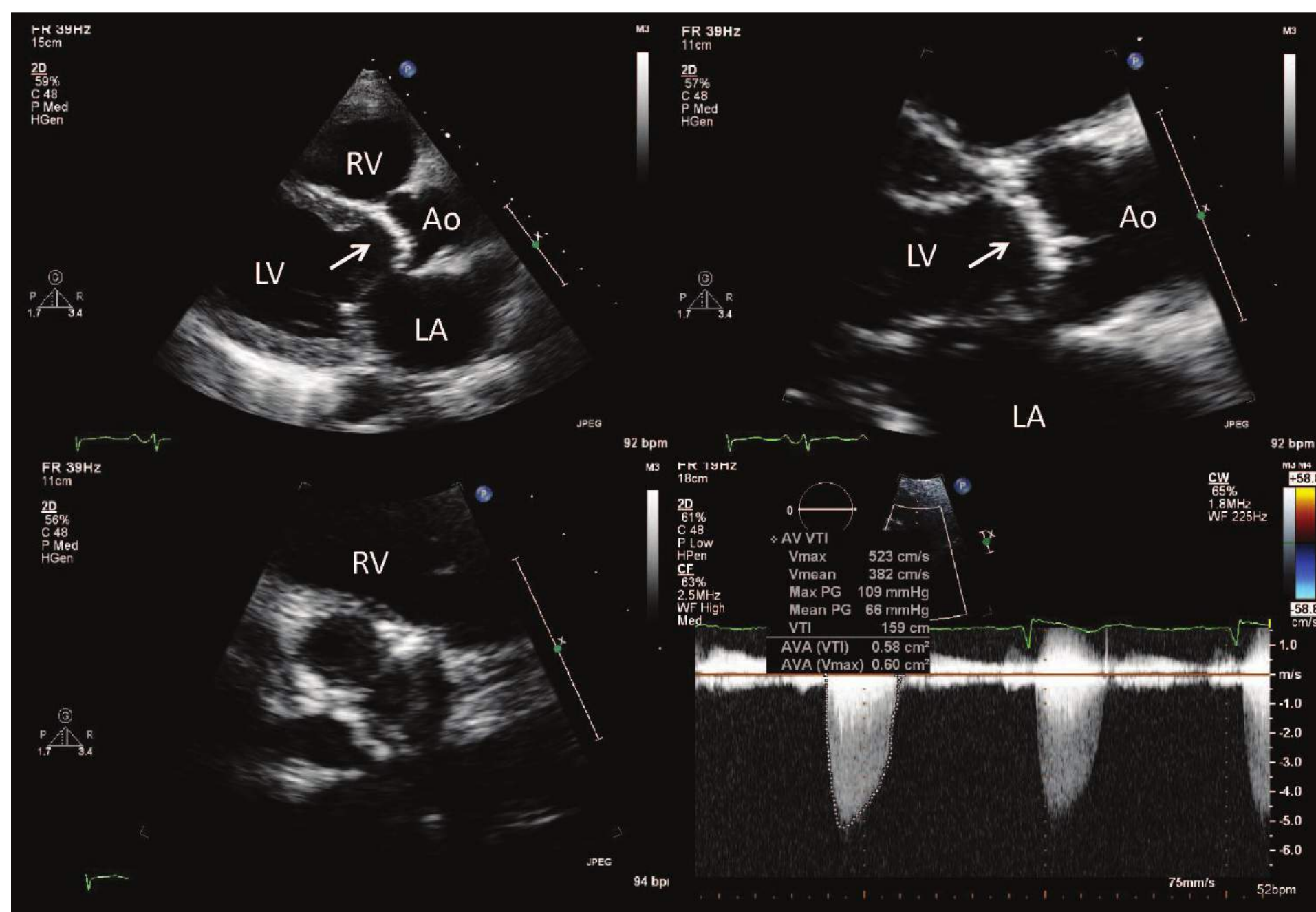


FIGURE 51-12

A 70-year-old patient with known cardiac murmur and progressive shortness of breath and a recent episode of syncope. Echocardiography shows severe calcific aortic stenosis. A heavily calcified aortic valve (arrow) is shown in the parasternal long-axis views (top panels) and short-axis view (bottom left). Doppler interrogation shows a peak transaortic velocity of 5.2 m/s consistent with a peak instantaneous gradient of 109 mmHg and a mean gradient of 66 mmHg, and a corresponding aortic valve area of $<0.6\text{ cm}^2$ (lower right). Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (See Videos 51-8, 51-9, and 51-10.)

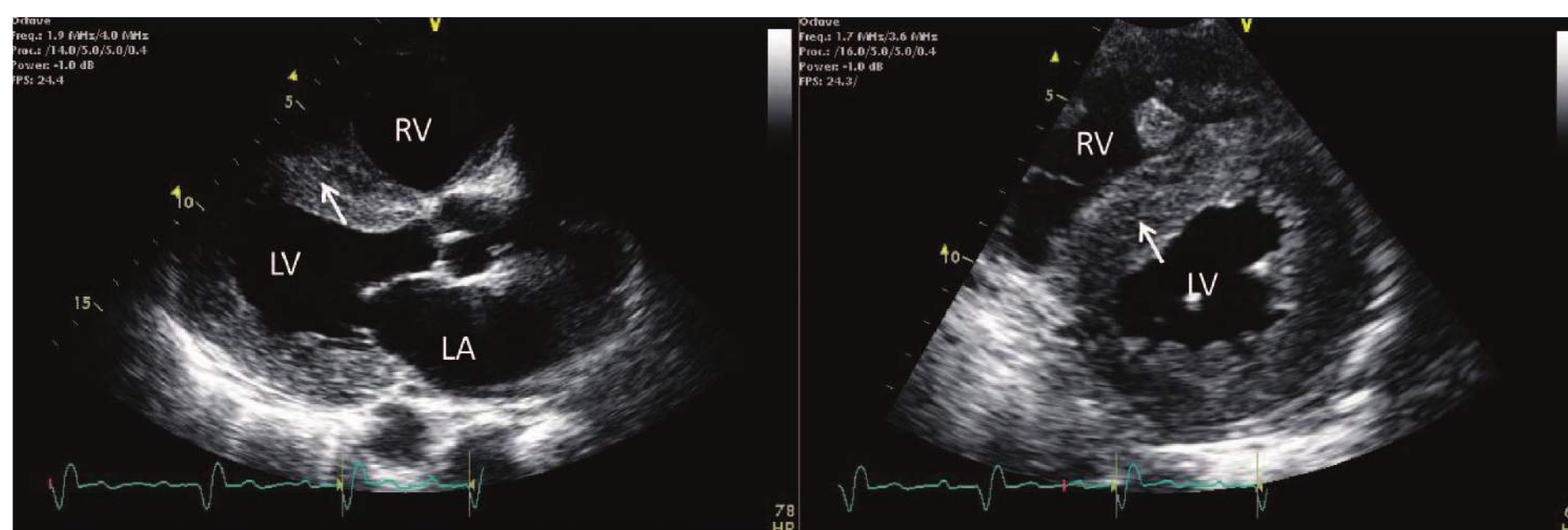


FIGURE 51-13

A 66-year-old patient with multiple myeloma and progressive shortness of breath. Echocardiography shows features typical of cardiac amyloidosis, including thickened myocardium with a “sparkly” appearance and left atrial enlargement.

Systolic function is mildly reduced, and diastolic function is severely reduced. LA, left atrium; LV, left ventricle; RV, right ventricle. (See Videos 51-11 and 51-12.)

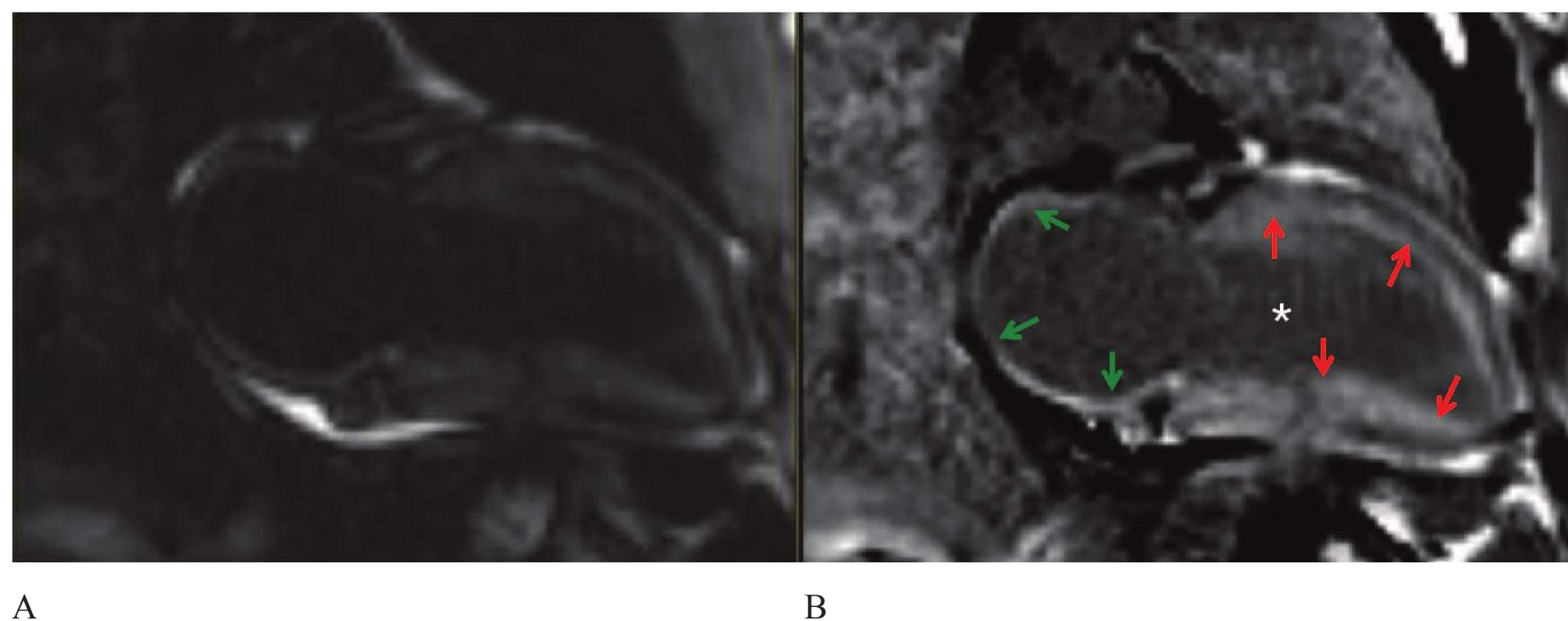


FIGURE 51-14

Magnetic resonance image with contrast enhancement in magnitude (A), and phase-sensitive reconstructed images (B) 5–10 min after injection of gadolinium in a patient with transthyretin (TTR)-mediated amyloidosis. The phase-sensitive reconstruction (B) enhances the region of abnormal collection of gadolinium, making gadolinium enhancement in the

ventricle (red arrows) and the atrium (green arrows) more prominent. Amyloidosis causes accumulation of abnormal interstitial proteins, which results in late gadolinium enhancement in a diffuse subendocardial pattern (red arrows). Blood pool signal is characteristically dark (asterisk) owing to sequestration of gadolinium into other organs.

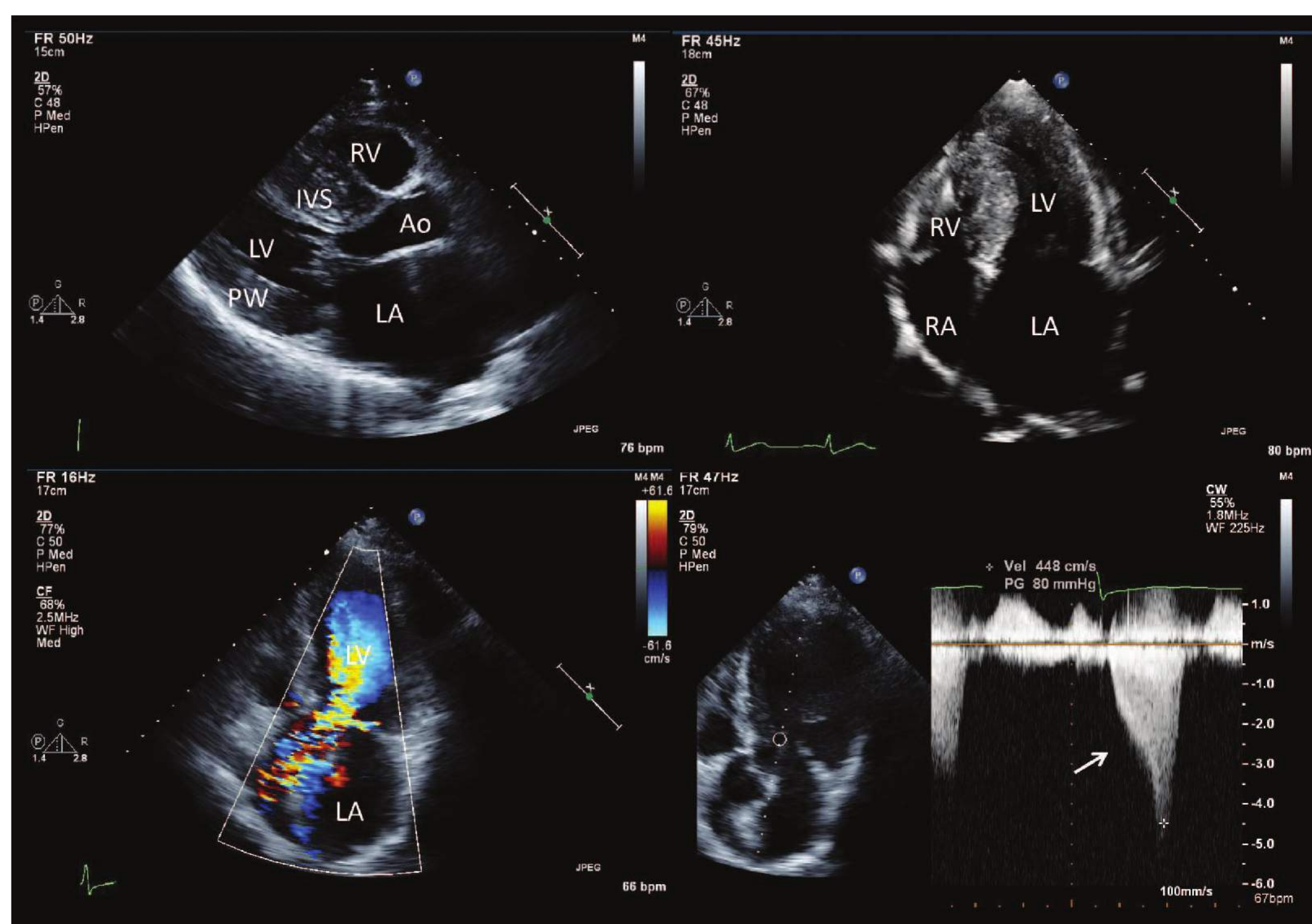


FIGURE 51-15

A 34-year-old woman with known cardiac murmur and syncope with a family history of sudden cardiac death. Echocardiogram shows classic findings of hypertrophic cardiomyopathy, including marked left ventricular wall thickness, particularly in the interventricular septum, notable in the parasternal long-axis view (upper left) and apical view (upper right). Note reverse septal

curvature in the apical view (upper left). There is substantial flow acceleration through the left ventricular outflow tract (lower left) with evidence of a late peaking systolic gradient (arrow, lower right) caused by outflow tract obstruction. Ao, aorta; IVS, interventricular septum; LA, left atrium; LV, left ventricle; PW, posterior wall; RV, right ventricle. (See Videos 51-13, 51-14, and 51-15.)

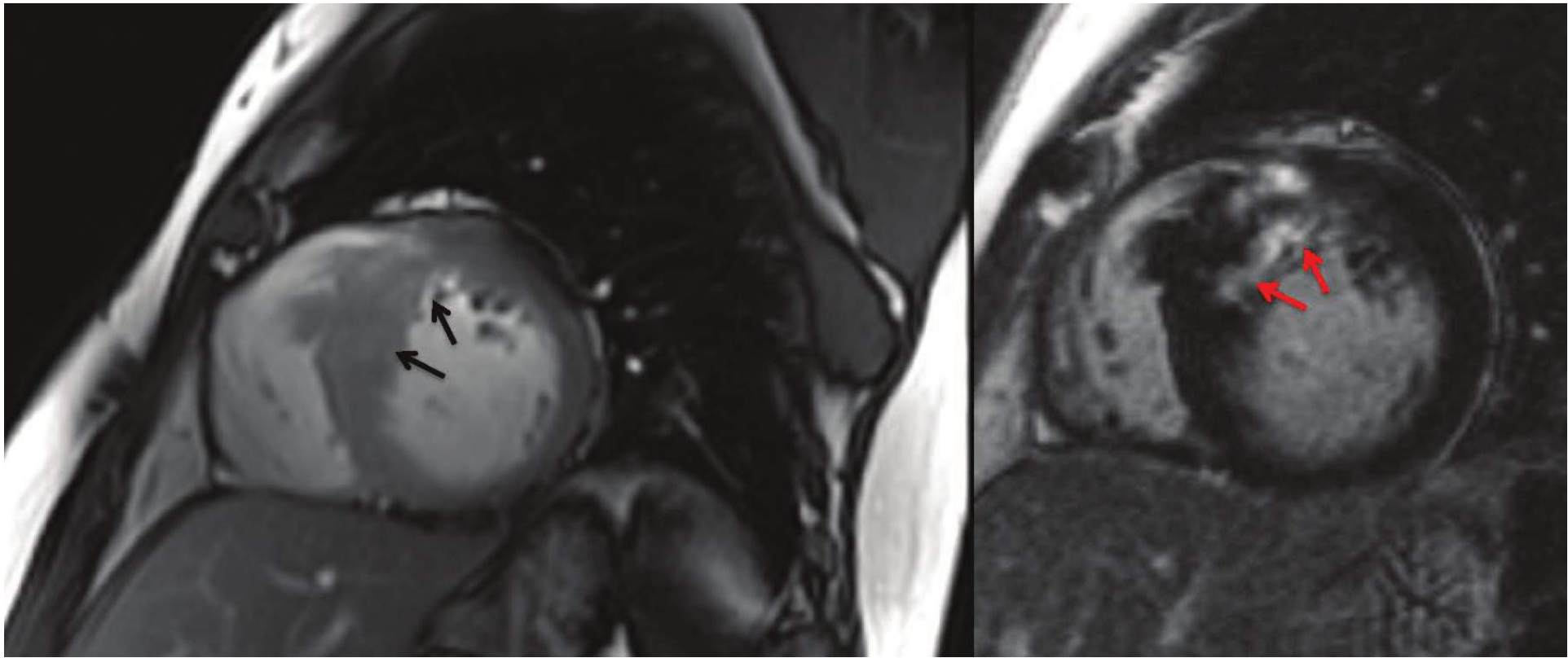


FIGURE 51-16

Magnetic resonance image with contrast enhancement in a patient with hypertrophic cardiomyopathy. Note the marked thickened anteroseptal wall (black arrows, left panel) consistent with asymmetric septal hypertrophy. After contrast is injected, this region demonstrated heterogeneous foci of contrast

enhancement (right panel, red arrows) consistent with myocardial fibrosis due to myofibril disarray in this condition. This typical enhancement pattern of hypertrophic cardiomyopathy is found in the areas of maximum wall thickness, typically at the antero-septum as in this case. (See Video 51-16.)

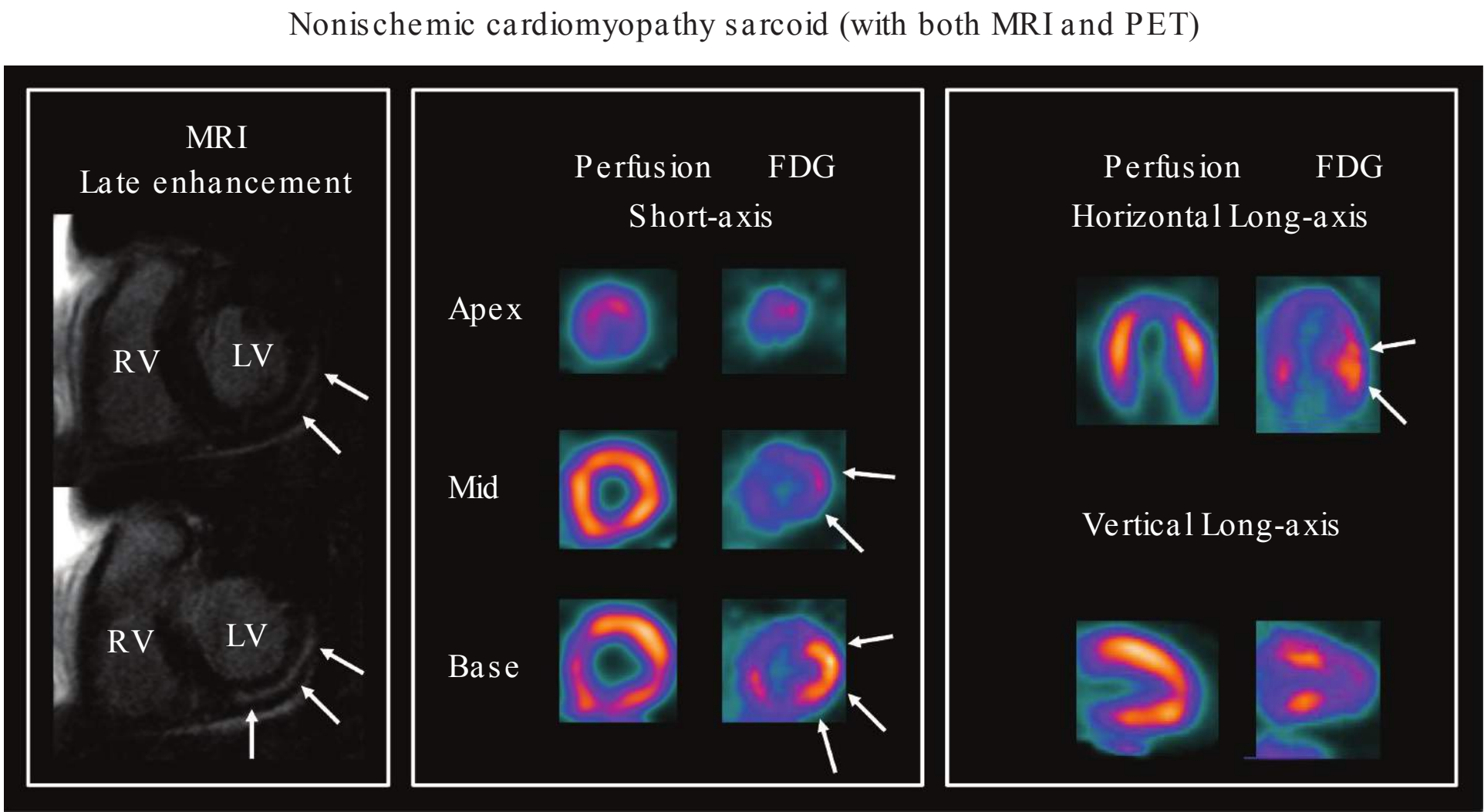


FIGURE 51-17

Late gadolinium enhancement cardiac magnetic resonance imaging (MRI) (left panel) and rest myocardial perfusion and fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) studies (middle and right panels) in a 48-year-old male with a complete heart block. The MRI images demonstrate a linear area of mid-wall late gadolinium

enhancement involving the inferior and inferolateral walls (arrows). The myocardial perfusion images were normal. However, the FDG images demonstrated a focal area of intense glucose uptake in the inferolateral wall, corresponding to the area of late enhancement on MRI. This is consistent with focal active sarcoidosis. LV, left ventricle; RV, right ventricle.

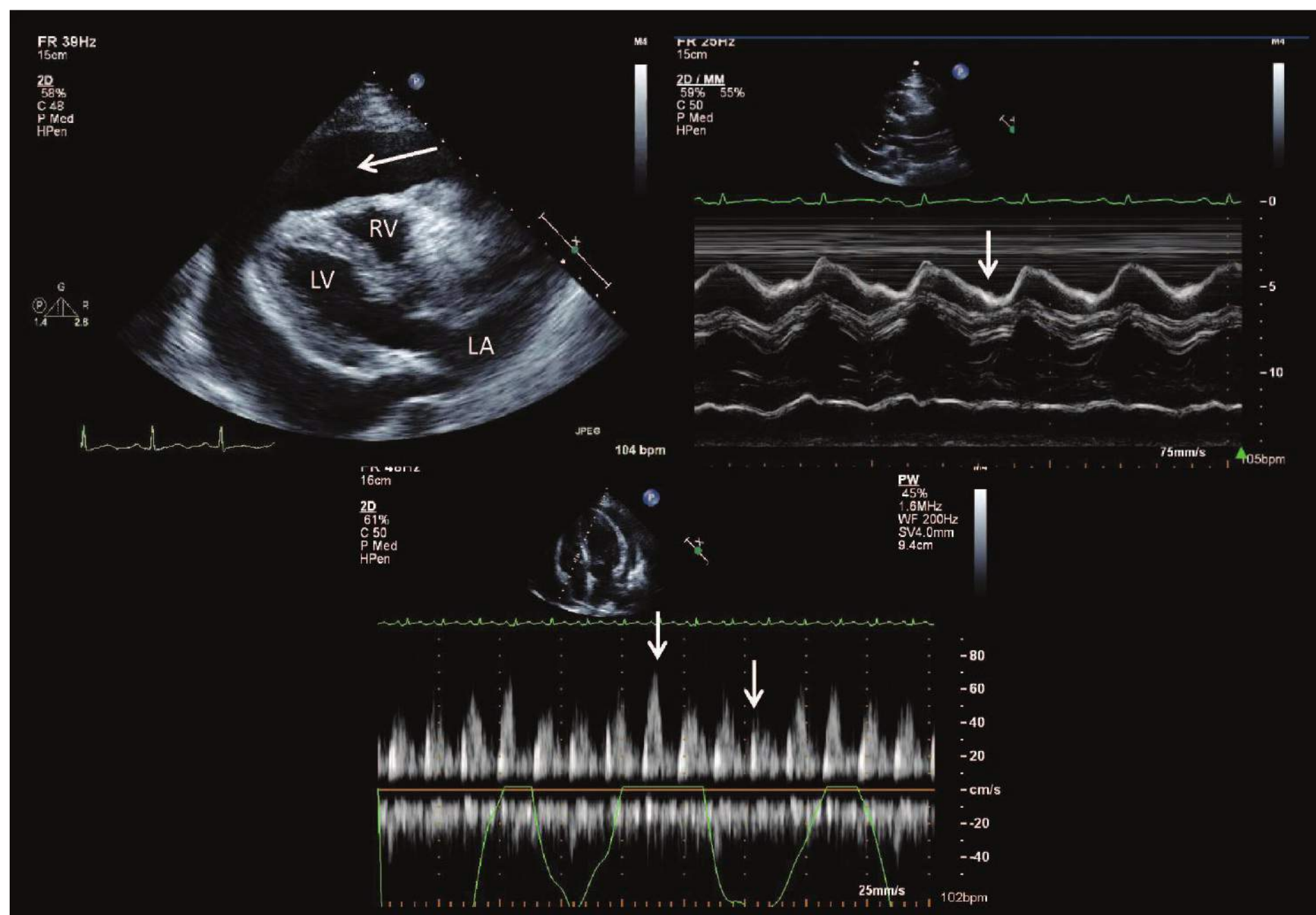


FIGURE 51-18

A 46-year-old patient with malignant melanoma who presents with acute shortness of breath. Echocardiogram reveals a large pericardial effusion (arrow, upper left) with evidence of cardiac tamponade. M-mode echocardiography (upper right) shows evidence

of collapse of the right ventricular free wall during diastole (arrow). Doppler echocardiography (lower panel) shows evidence of respiratory flow variation, consistent with a pulsus paradoxus. LA, left atrium; LV, left ventricle; RV, right ventricle. (See Video 51-17.)

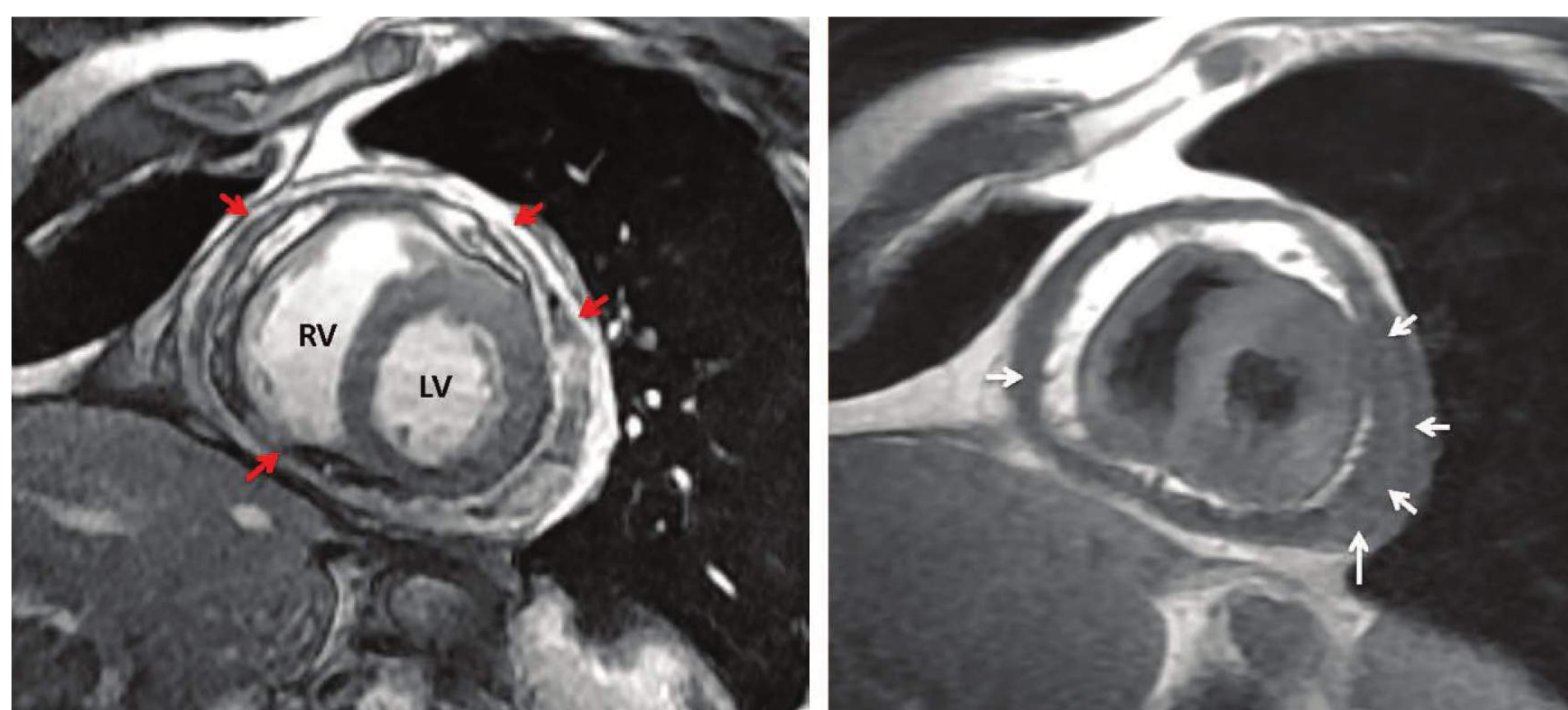


FIGURE 51-19

Diffuse pericardial thickening (left; red arrows) and circumferential effusion (right; white arrows) associated with effusive-constrictive pericarditis. Effusive-constrictive pericarditis is a progressive condition that has varying degrees of hemodynamic consequences due initially to the collection of pericardial

fluid and ultimately to pericardial constriction. It is typically suspected in cases where pericardiocentesis fails to normalize intracardiac pressures. In this example, pericardial fluid analysis resulted in a sterile exudate of leukocytes and erythrocytes. LV, left ventricle; RV, right ventricle.

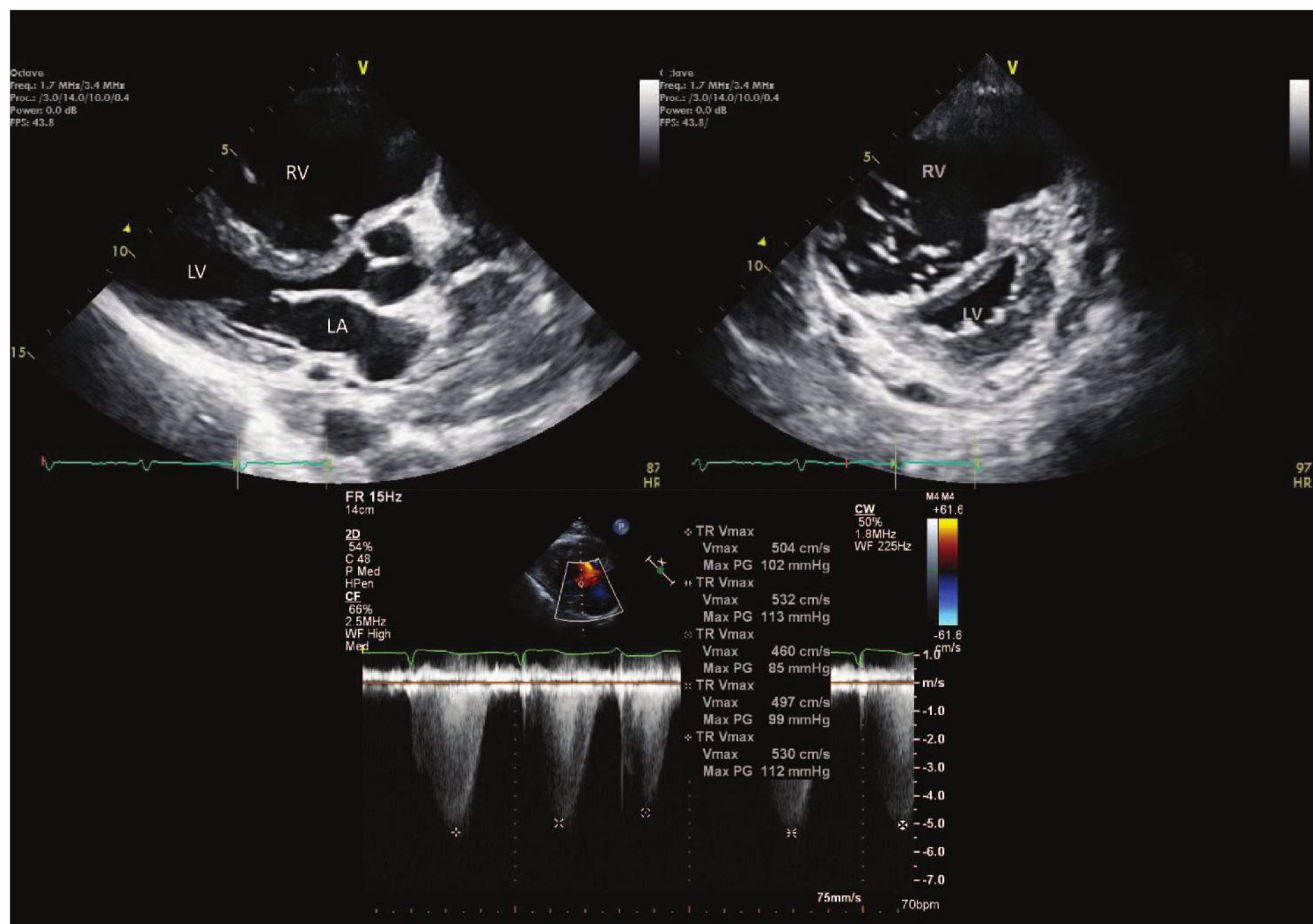
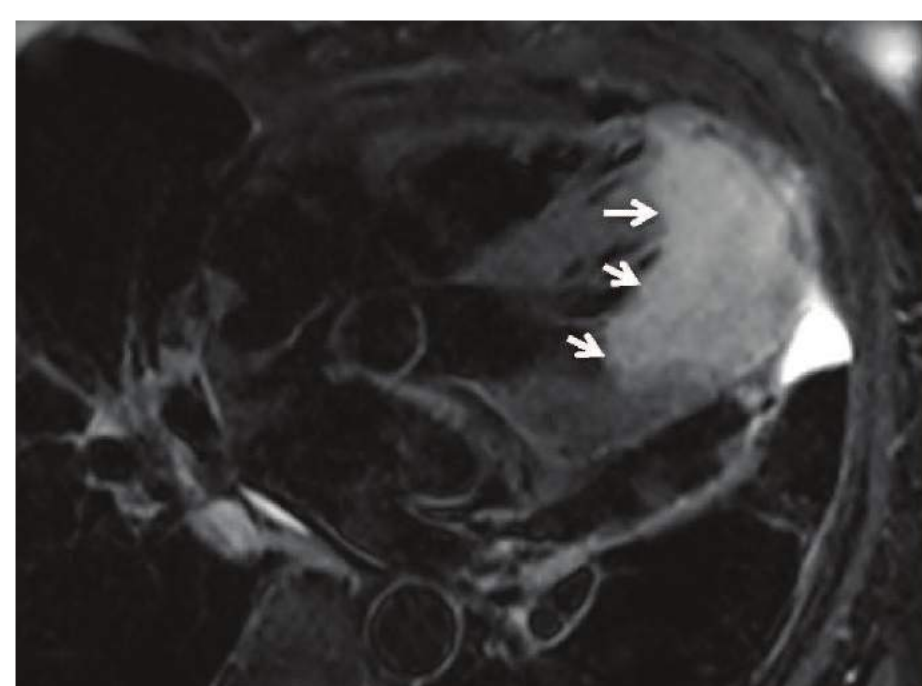
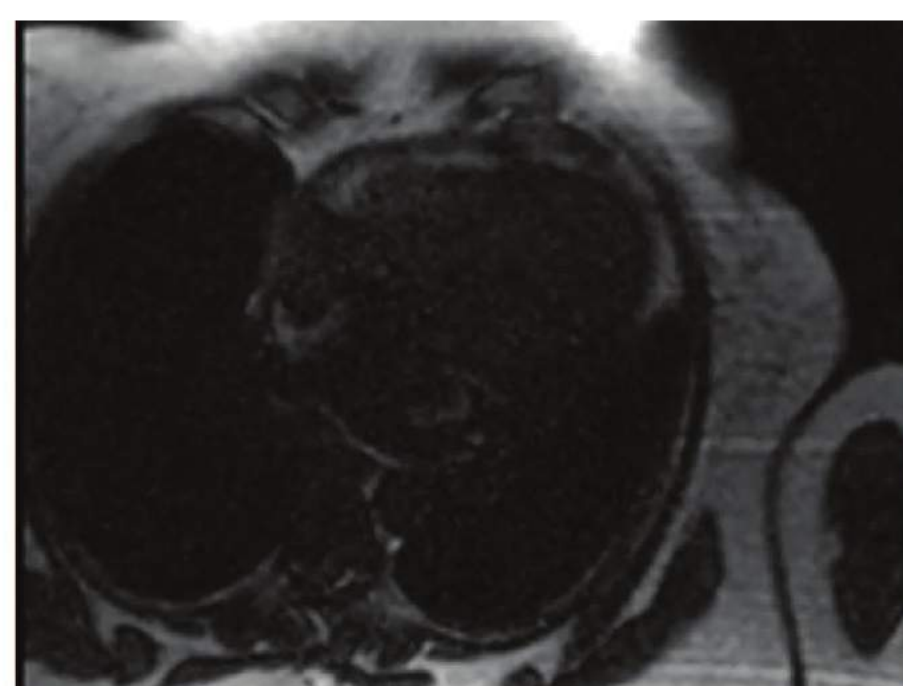


FIGURE 51-20

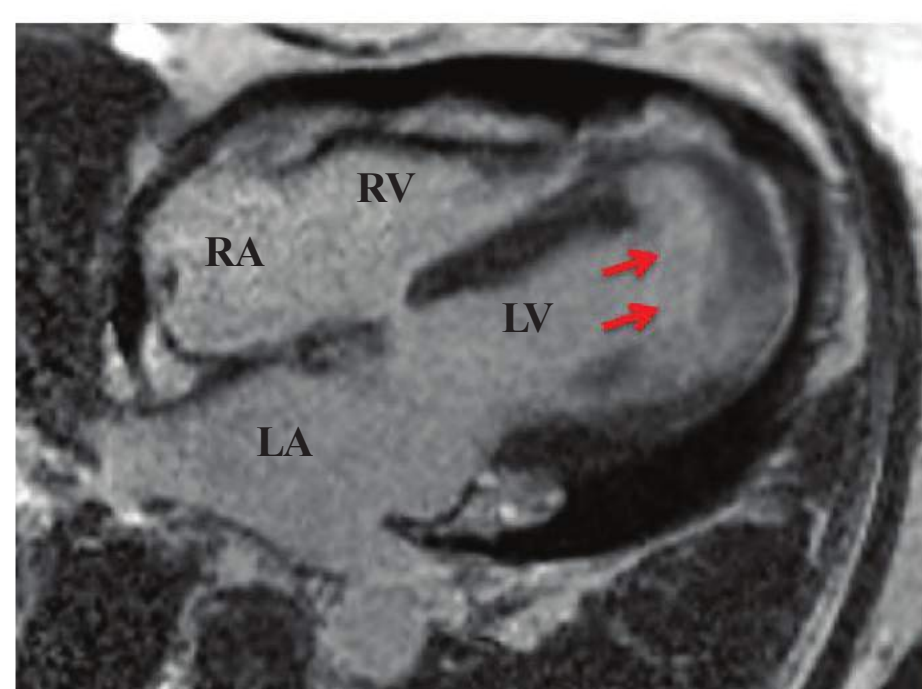
A 48-year-old woman with severe idiopathic pulmonary hypertension. Echocardiography reveals evidence of marked right ventricular volume and pressure overload as evidenced by enlarged right ventricle (upper left and right), small left ventricle (upper left and upper right), and flattening of the interventricular septum (D-shaped septum) in systole and diastole (upper right). Tricuspid regurgitation velocity, which reflects the pressure gradient between the right ventricle and the left ventricle, is markedly elevated at 5 m/s, consistent with a right ventricle to right atrial pressure gradient of 100 mmHg, which is consistent with systemic right-sided pressures. LA, left atrium; LV, left ventricle; RV, right ventricle. (See Videos 51-18 and 51-19.)



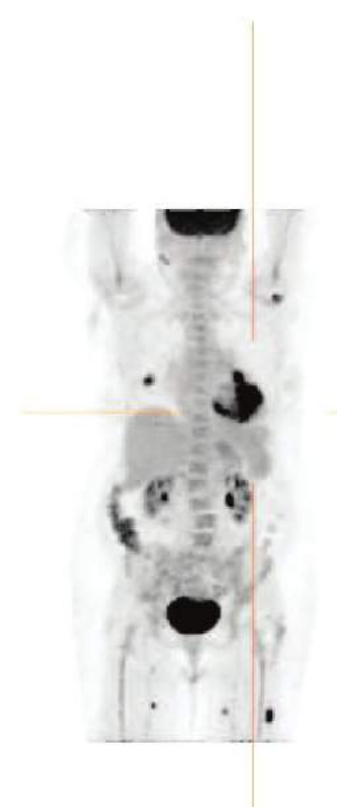
A



B



C



D

FIGURE 51-21

Metastatic cardiac tumor diagnosed by cardiac magnetic resonance (MR) in a patient who presented with chest pain and inferior ST elevation. Left heart catheterization was normal. Cardiac MR demonstrates extensive myocardial edema (A, white arrows) with marked reduction in first perfusion (B) and accumulation of gadolinium within the cardiac mass 10–15 min after injection

of gadolinium (C, red arrows). D. Positron emission tomography scan showed increased fluorodeoxyglucose uptake in a lung mass as well as in the cardiac mass, consistent with cardiac metastasis. Biopsy of the lung mass revealed adenocarcinoma of the lung. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (See Videos 51-20 and 51-21.)

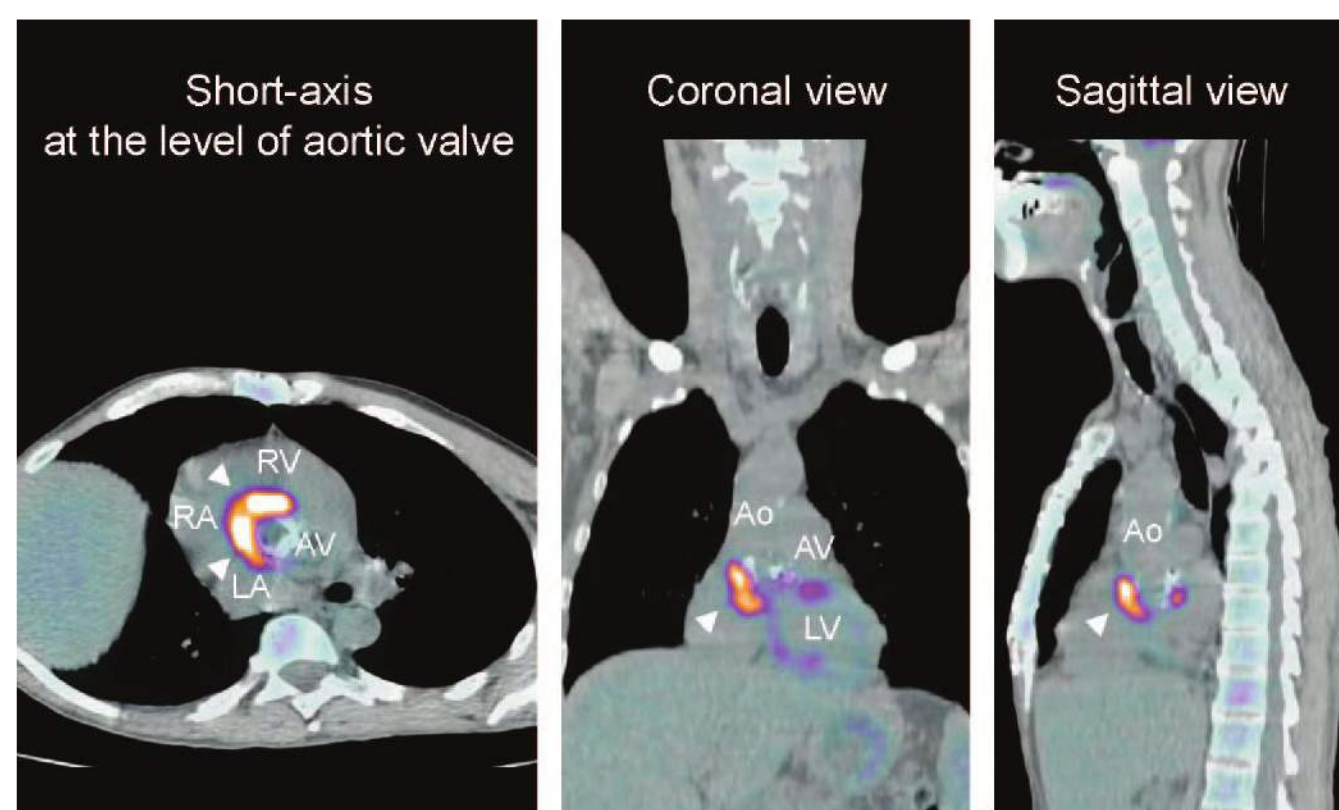


FIGURE 51-22

Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in a 52-year-old male with a prior aortic valve replacement who presented with fever and was found to have *Haemophilus parainfluenzae* bacteremia. The multiplanar reformatted fused PET/CT images demonstrate intense

FDG uptake surrounding the aortic valve prosthesis (arrowheads), compatible with a paravalvular abscess. The patient was found to have purulent fluid around the valve during surgery, and he underwent an aortic valve replacement. Ao, aorta; AV, aortic valve; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

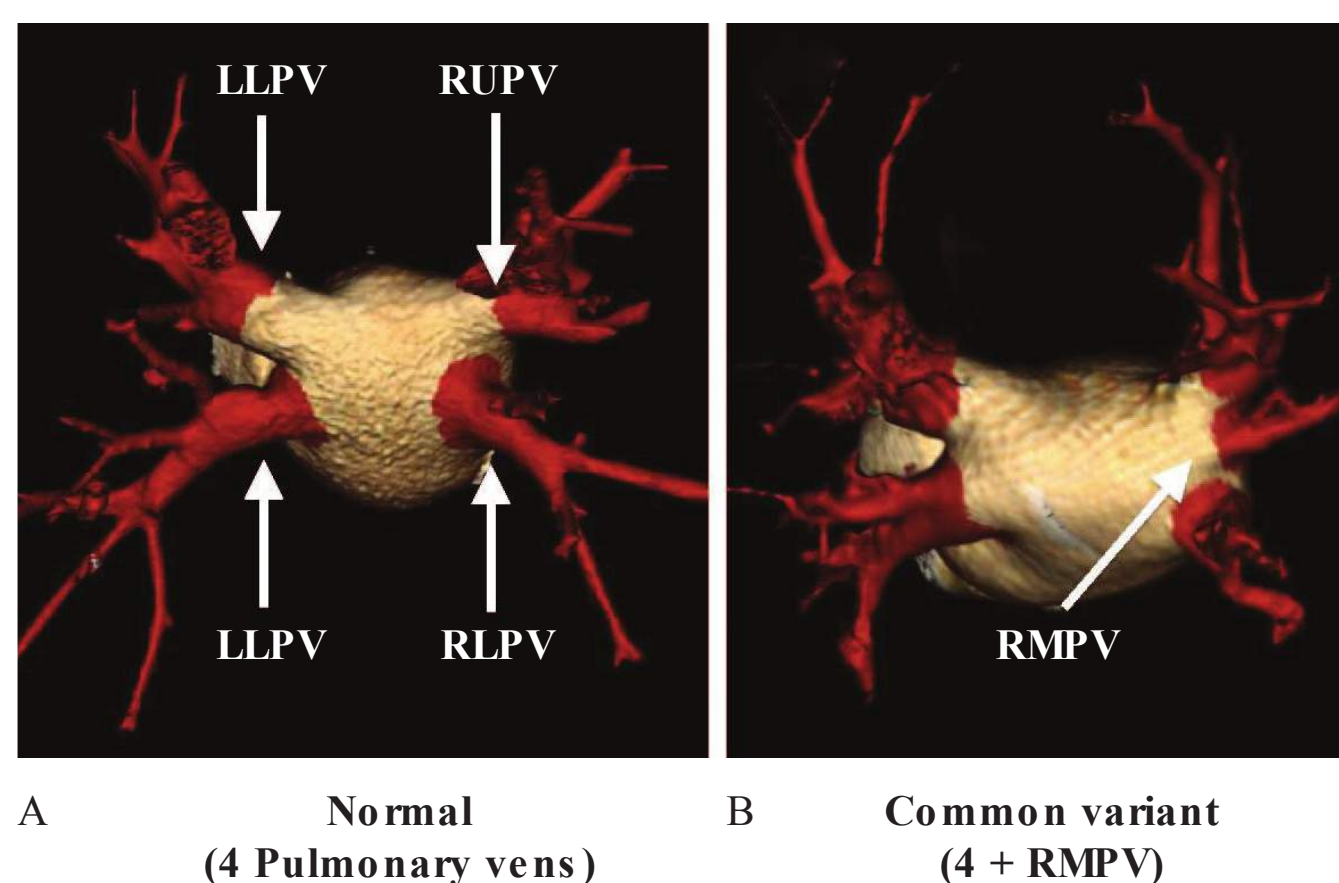


FIGURE 51-23

Cardiac computed tomography (CT) pulmonary vein mapping in a 62-year-old male with symptomatic, paroxysmal atrial fibrillation referred for cardiac CT for pulmonary vein mapping prior to planned pulmonary vein isolation. Three-dimensional image reconstruction, demonstrating (A) normal

pulmonary vein anatomy and (B) common variant with presence of separate right middle pulmonary vein (RMPV) ostium. LLPV, left lower pulmonary vein; LUPV, left upper pulmonary vein; RLPV, right lower pulmonary vein; RUPV, right upper pulmonary vein.

Videos can be accessed via the following link:

<https://www.mhprofessional.com/mediacenter/>

Video 51–1. Echocardiography in the evaluation of acute myocardial infarction.

Video 51–2. Echocardiography in the evaluation of acute myocardial infarction.

Video 51–3. Stress echocardiography for suspected CAD.

Video 51–4. Stress echocardiography for suspected CAD.

Video 51–5. CMR stress myocardial perfusion images.

Video 51–6. CMR stress myocardial perfusion images.

Video 51–7. A Case of viability assessment in a patient with inferior myocardial infarction.

Video 51–8. Echocardiography for evaluation of the severity of aortic stenosis.

Video 51–9. Echocardiography for evaluation of the severity of aortic stenosis.

Video 51–10. Echocardiography for evaluation of the severity of aortic stenosis.

Video 51–11. Utility of MRI to evaluate for cardiac amyloidosis.

Video 51–12. Utility of MRI to evaluate for cardiac amyloidosis.

Video 51–13. Utility of echocardiography to evaluate suspected hypertrophic cardiomyopathy.

Video 51–14. Utility of echocardiography to evaluate suspected hypertrophic cardiomyopathy.

Video 51–15. Utility of echocardiography to evaluate suspected hypertrophic cardiomyopathy.

Video 51–16. Classic MR findings in a patient with hypertrophic cardiomyopathy.

Video 51–17. Utility of echocardiography to evaluate cardiac involvement.

Video 51–18. Classic echocardiographic findings.

Video 51–19. Classic echocardiographic findings.

Video 51–20. Metastatic cardiac tumor.

Video 51–21. Metastatic cardiac tumor.

CHAPTER 52

ATLAS OF CARDIAC ARRHYTHMIAS

Ary L. Goldberg

The electrocardiograms in this atlas supplement those illustrated in **Chaps. 15 and 17**. The interpretations emphasize findings of specific teaching value.

All of the figures are adapted from cases in ECG Wave-Maven, Copyright 2003, Beth Israel Deaconess Medical Center, <http://ecg.bidmc.harvard.edu>.

The abbreviations used in this chapter are as follows:

- AF—atrial fibrillation
- AV—atrioventricular
- LBBB—left bundle branch block
- LV—left ventricular
- LVH—left ventricular hypertrophy
- MI—myocardial infarction
- NSR—normal sinus rhythm
- RBBB—right bundle branch block
- VT—ventricular tachycardia
- WPW—Wolf -Parkinson-White

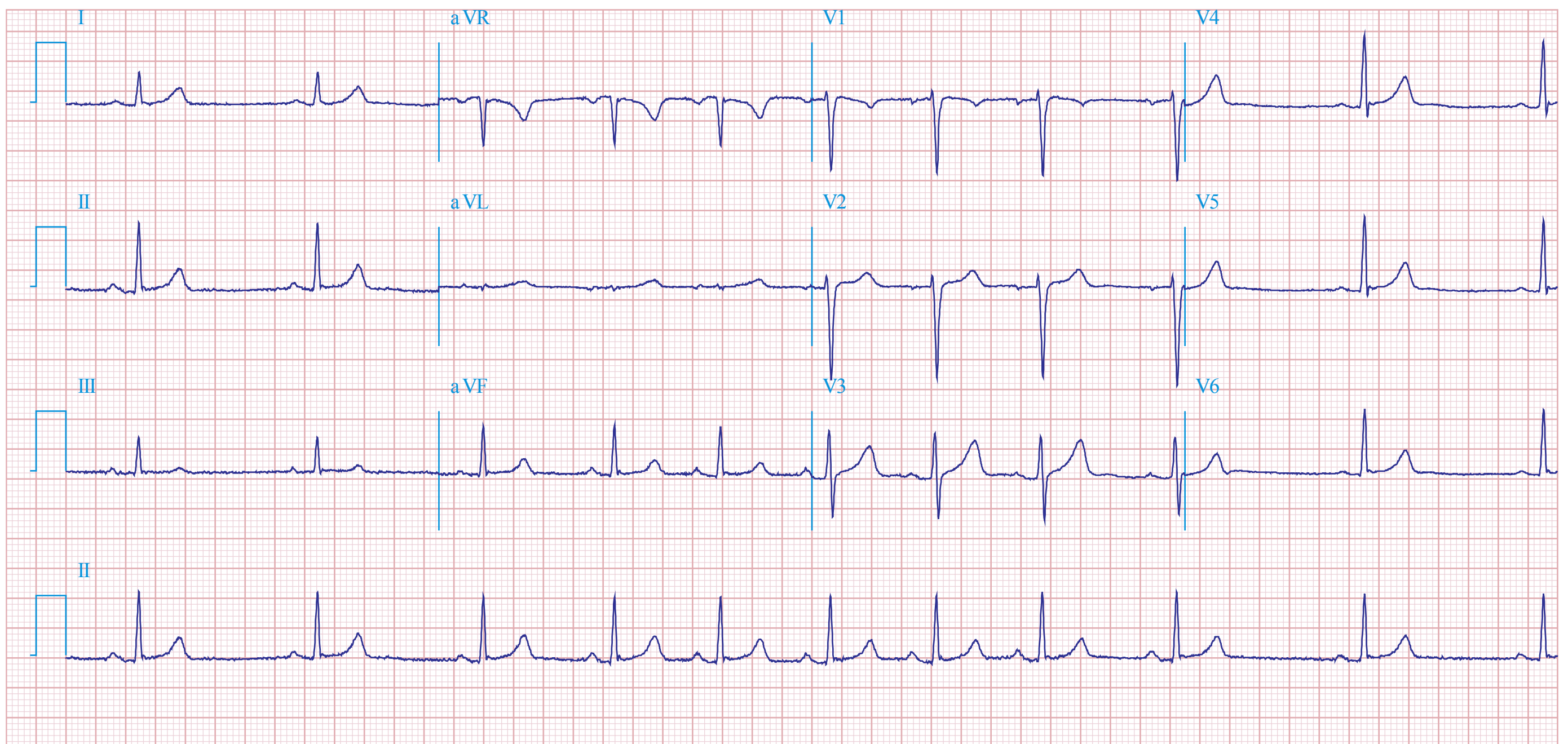


FIGURE 52-1

Respiratory sinus arrhythmia, a physiologic finding in a healthy young adult. The rate of the sinus pacemaker is relatively slow at the beginning of the strip during expiration, then

accelerates during inspiration and slows again with expiration. Changes are due to cardiac vagal tone modulation with breathing.

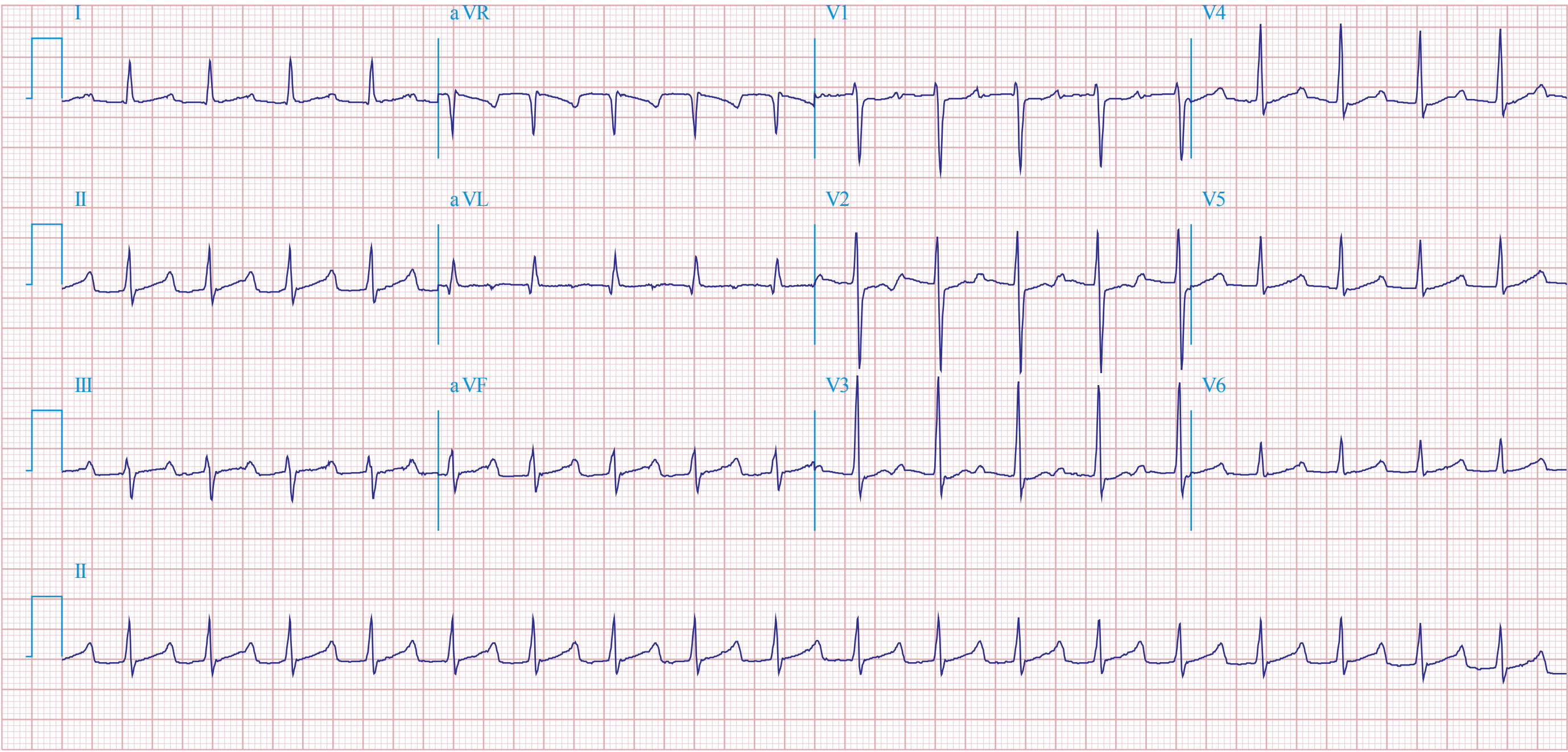


FIGURE 52-2
Sinus tachycardia (110/min) with **first-degree** AV “block” (conduction delay) with PR interval = 0.28 s. The P wave is visible after the ST-T wave in V₁–V₃ and superimposed on the

T wave in other leads. Atrial (nonsinus) tachycardias may produce a similar pattern, but the rate is usually faster.

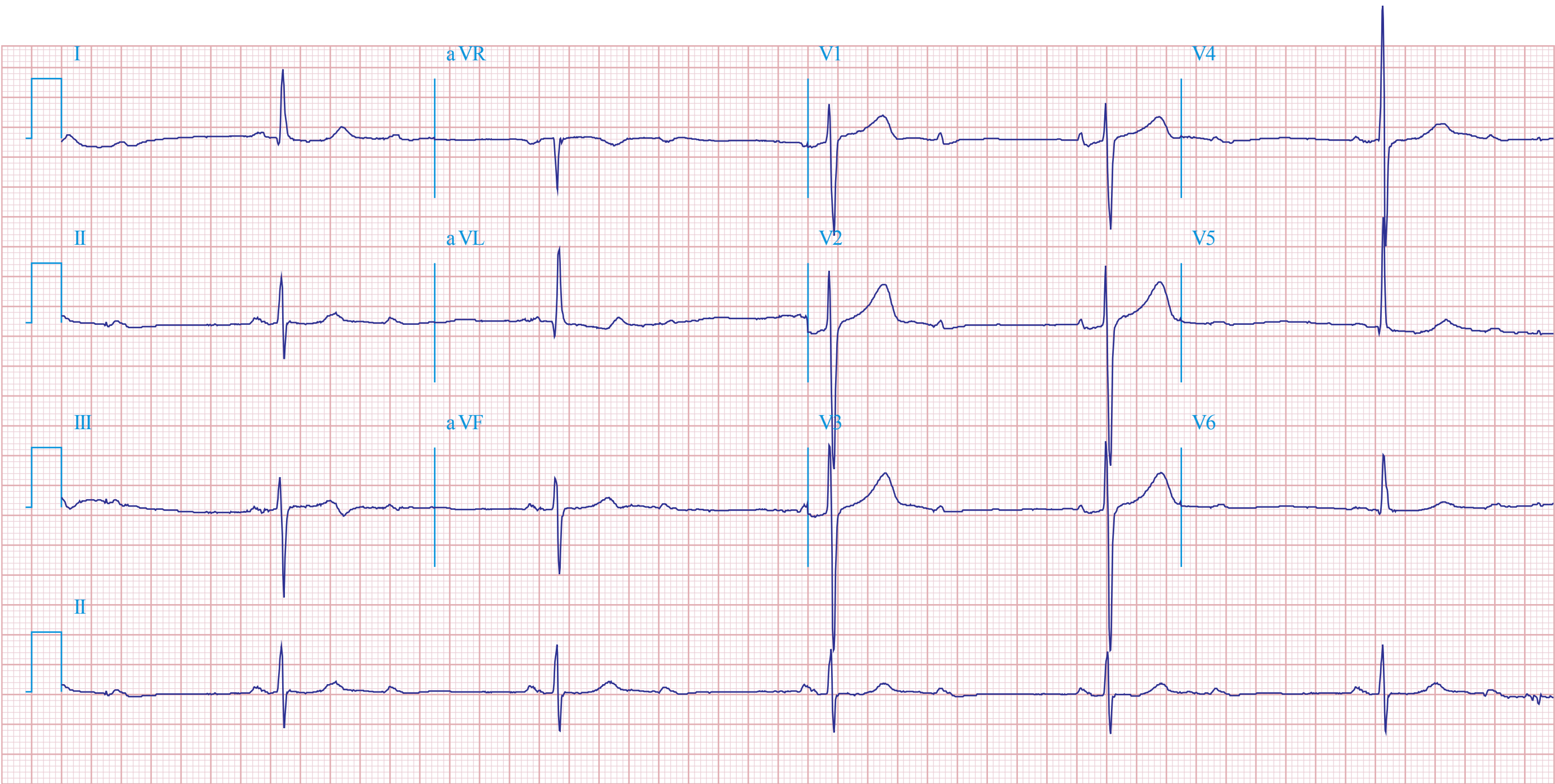


FIGURE 52-3
Sinus rhythm (P wave rate about 60/min) with 2:1 AV (second-degree) block causing marked bradycardia (ventricular rate of about 30/min). LVH is also present, along with left atrial abnormality.

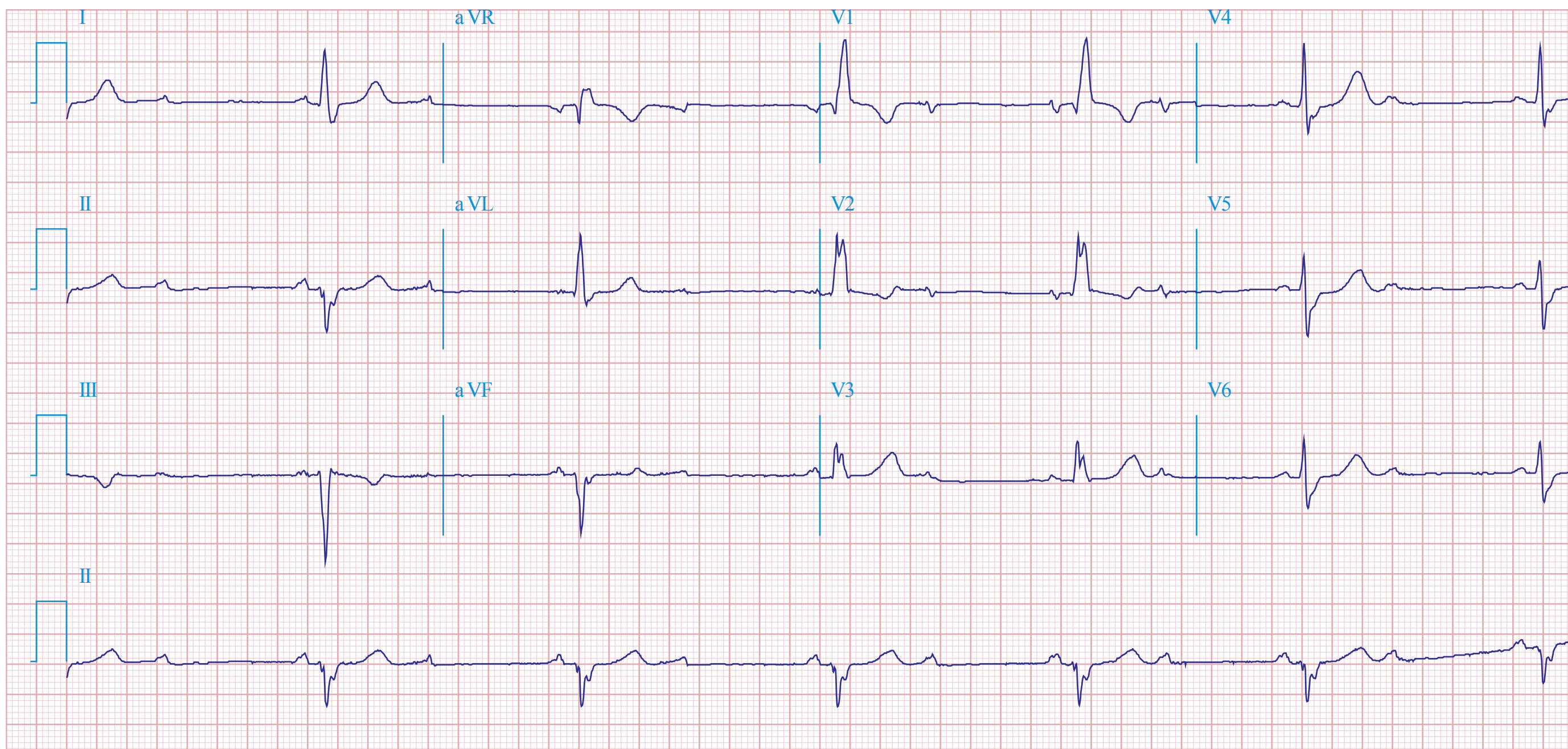


FIGURE 52-4

Sinus rhythm (P wave rate about 60/min) with 2:1 (second-degree) AV block yielding a ventricular (pulse) rate of about 30/min. Left atrial abnormality. RBBB with left anterior fascicular block. Possible inferior MI.

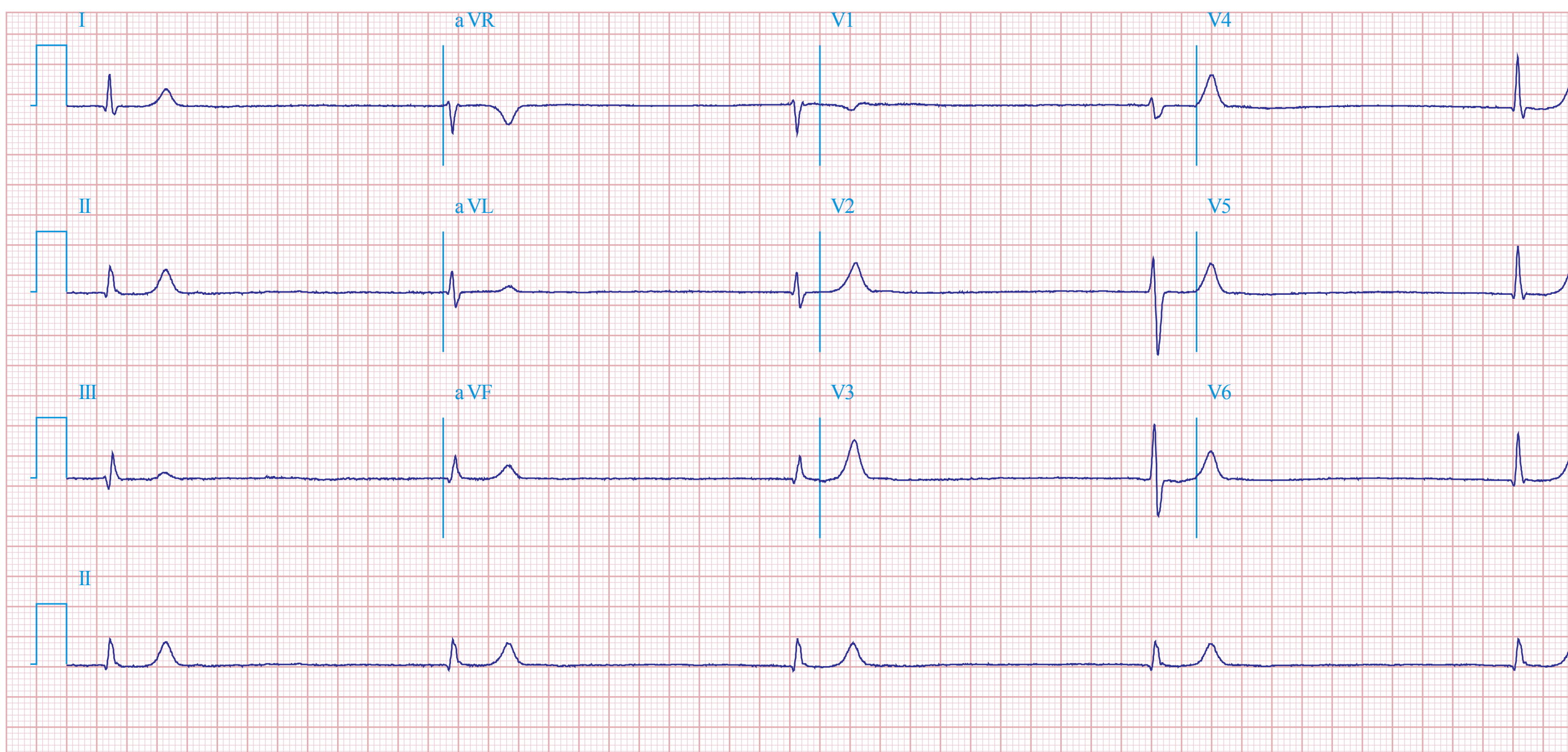


FIGURE 52-5

Marked junctional bradycardia (25 beats/min). Rate is regular with a flat baseline between narrow QRS complexes, without evident P waves. Patient was on atenolol, with

possible underlying sick sinus syndrome. The serum potassium was slightly elevated at 5.5 mEq/L.

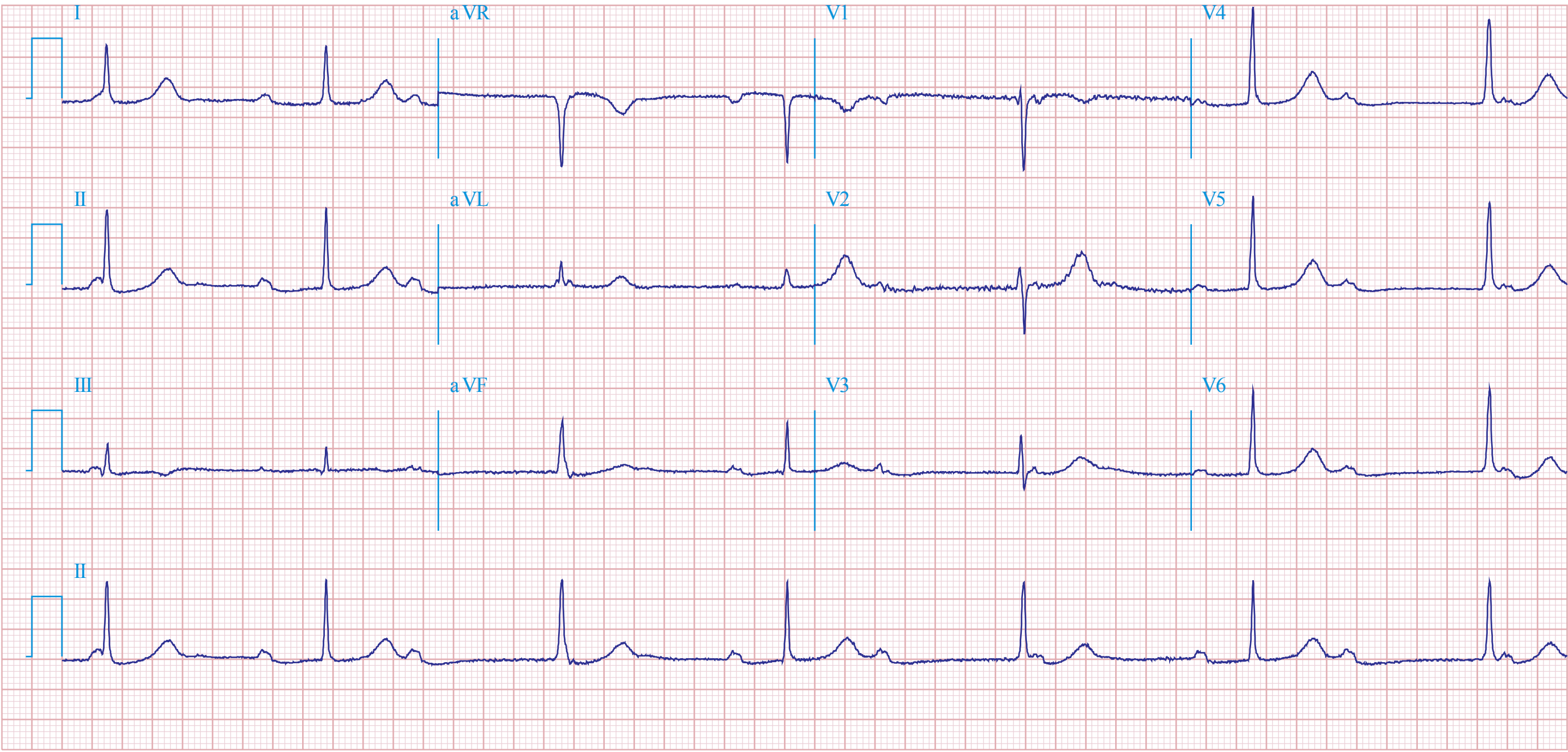


FIGURE 52-6
Sinus rhythm at a rate of 64/min (P wave rate) with third-degree (complete) AV block yielding an effective heart (pulse) rate of 40/min. The slow, narrow QRS complexes indicate an AV junctional escape pacemaker. Left atrial abnormality.

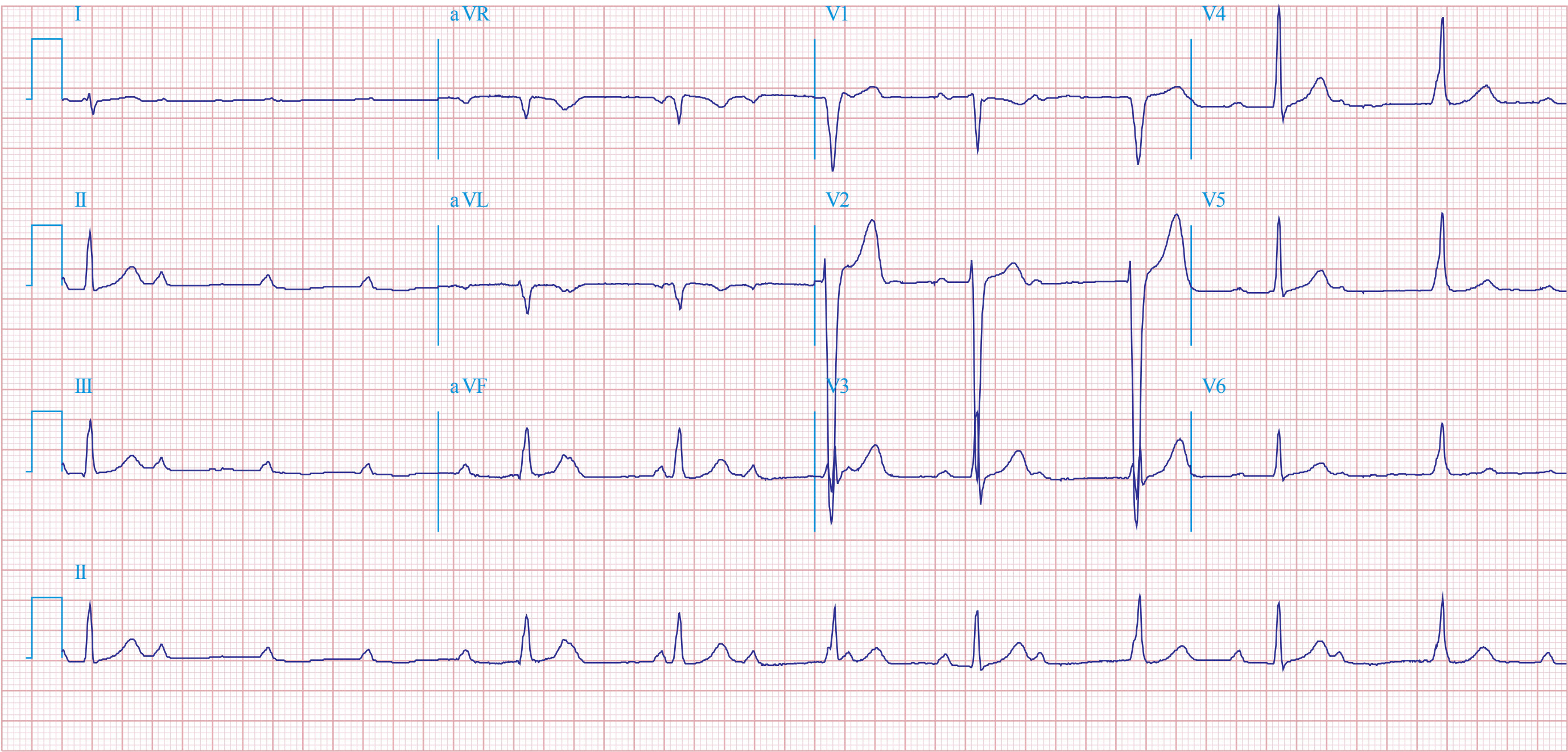


FIGURE 52-7
Sinus rhythm at a rate of 90/min with advanced second-degree AV block and possible transient complete heart block with Lyme carditis.

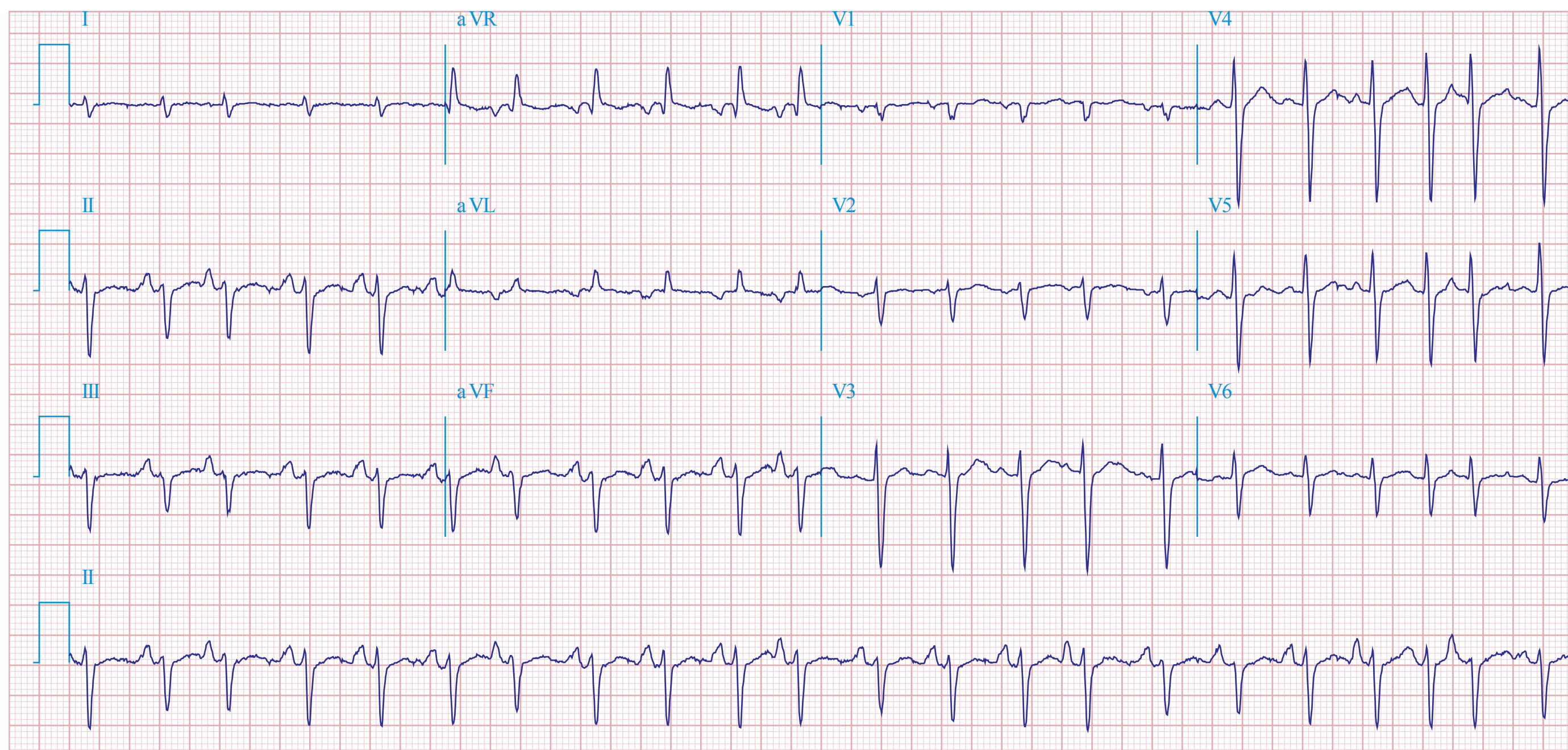


FIGURE 52-8

Multifocal atrial tachycardia with varying P-wave morphologies and P-P intervals; right atrial overload with peaked P waves in II, III, and aVF (with vertical P-wave axis); superior QRS

axis; slow R-wave progression with delayed transition in precordial leads in patient with severe chronic obstructive lung disease.

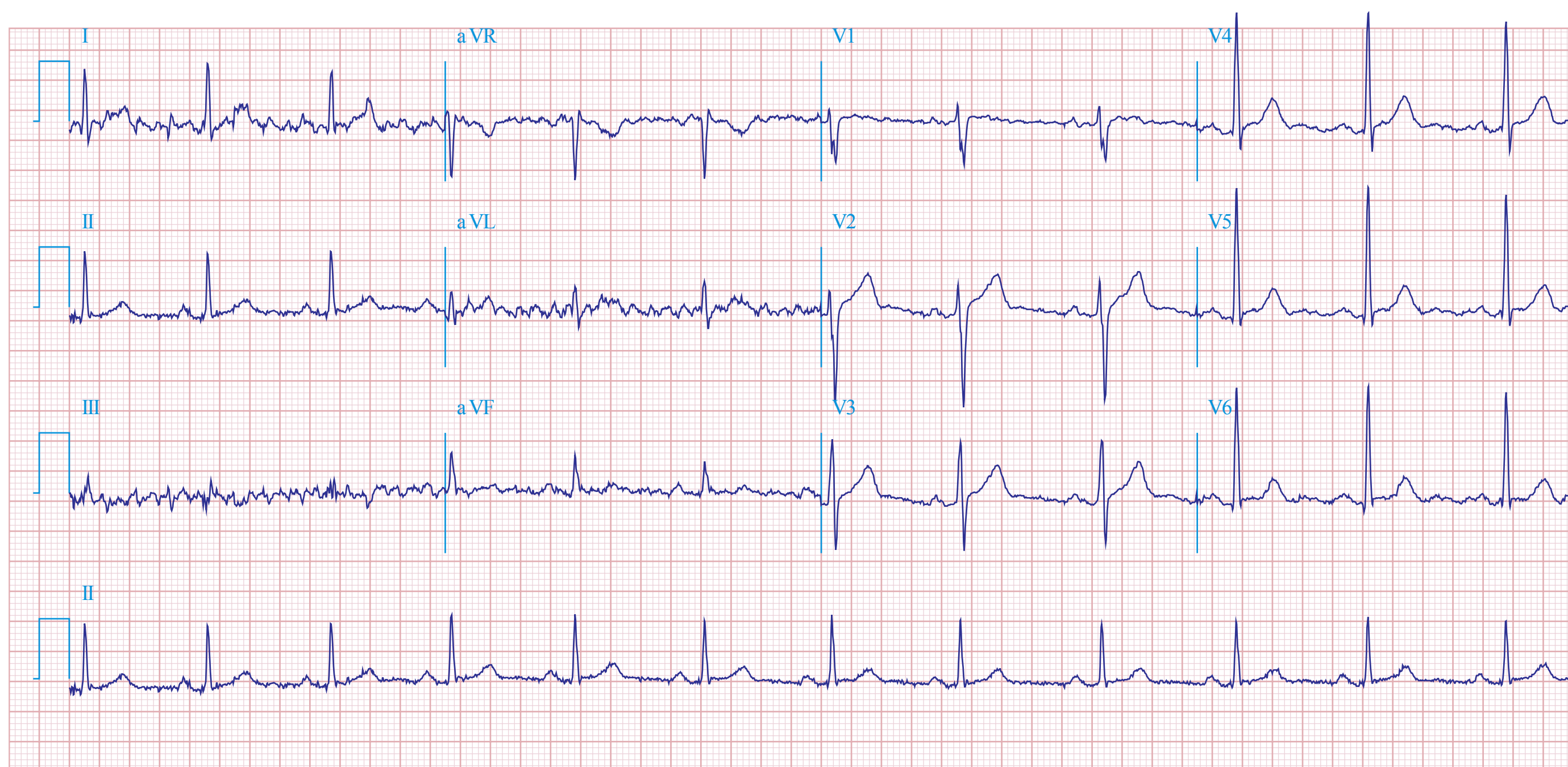


FIGURE 52-9

NSR in a patient with Parkinson's disease. Tremor artifact, best seen in limb leads. This tremor artifact may sometimes be confused with atrial flutter/fibrillation. Borderline voltage criteria for LVH are present.

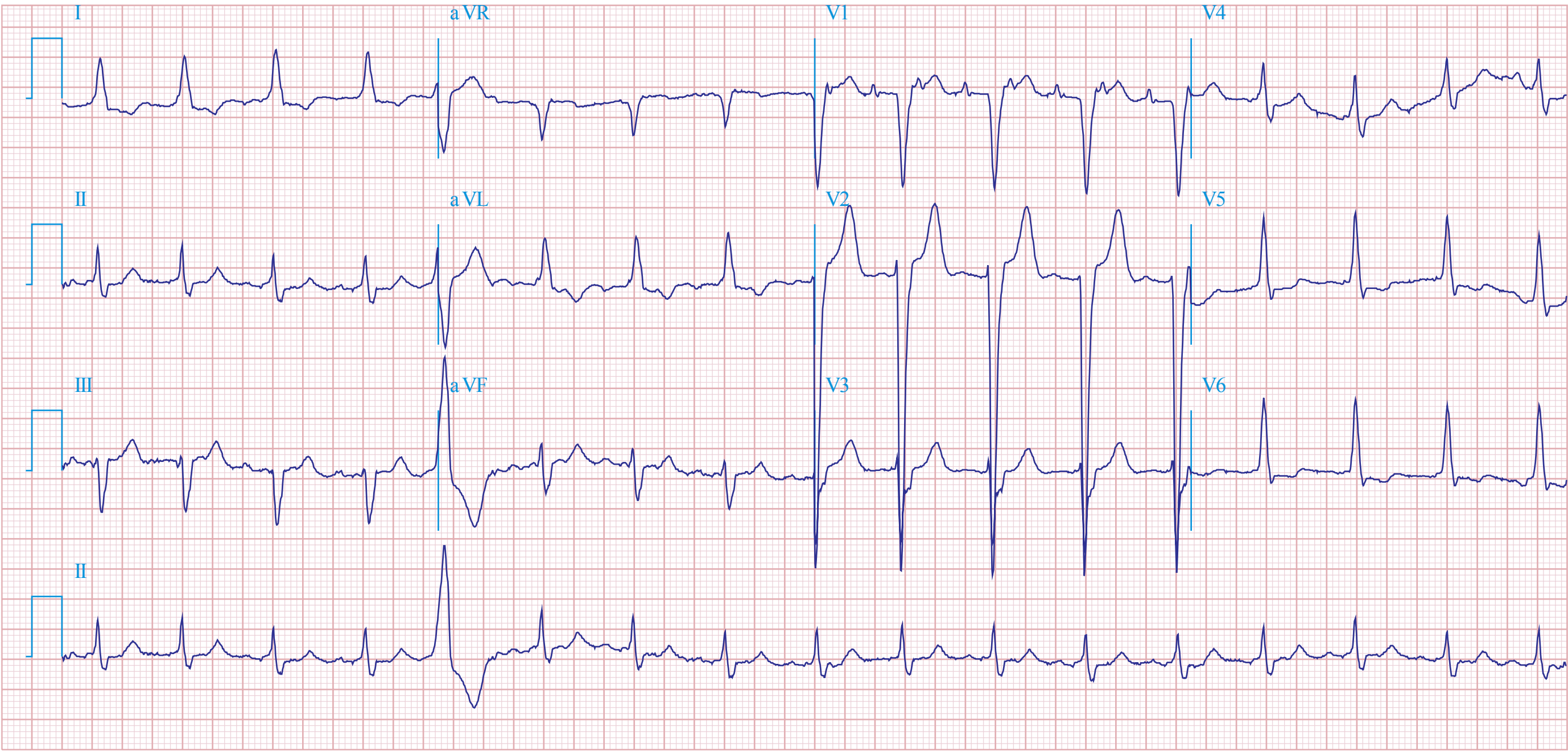


FIGURE 52-10
Atrial tachycardia with atrial rate of about 200/min (note lead V₁), 2:1 AV block (conduction), and one premature ventricular complex. Also present: LVH with intraventricular conduction delay and slow precordial R-wave progression (cannot rule out prior anterior MI).

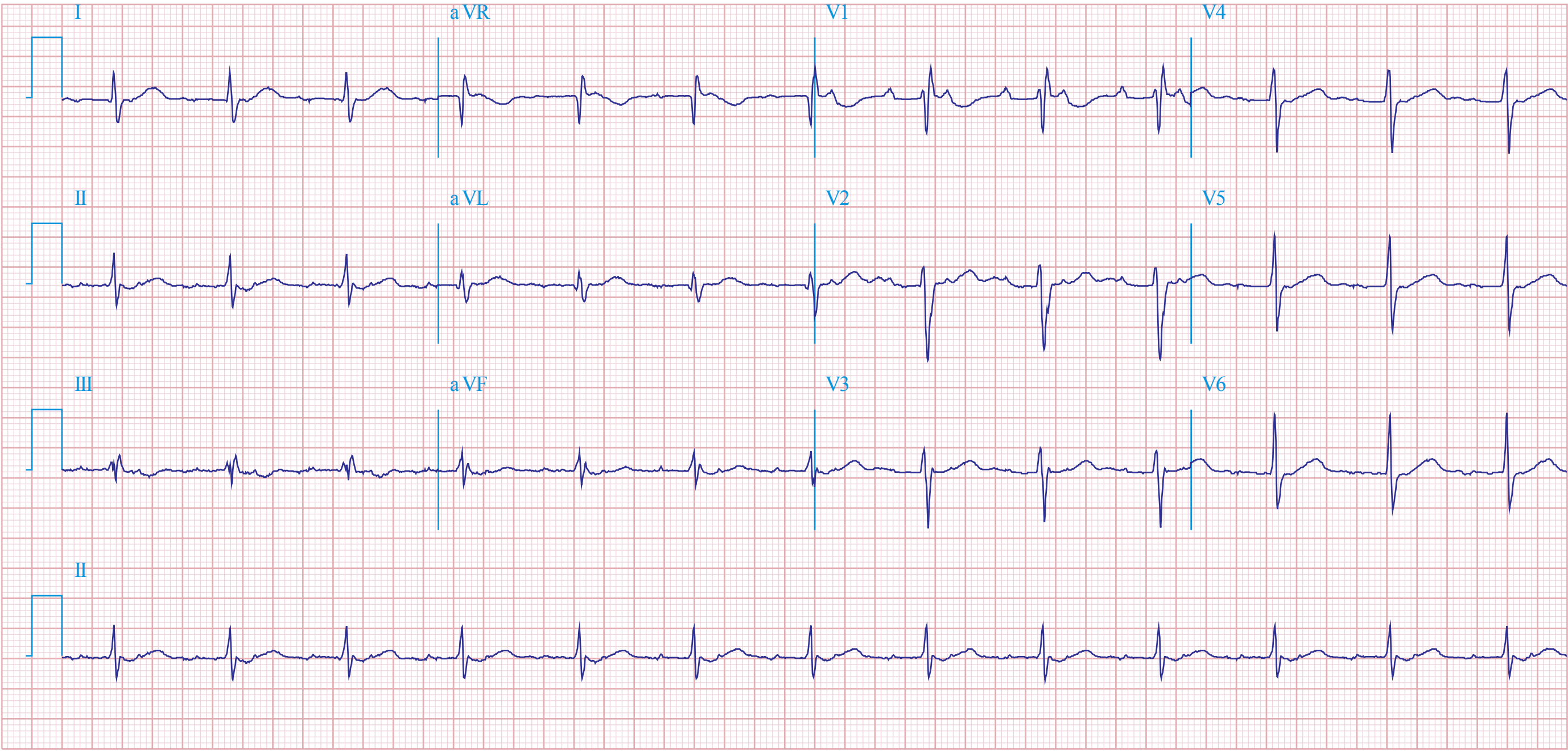


FIGURE 52-11
Atrial tachycardia with 2:1 block. P-wave rate is about 150/min, with ventricular (QRS) rate of about 75/min. The nonconducted (“extra”) P waves just after the QRS complex are best seen in lead V₁. Also, note incomplete RBBB and borderline QT prolongation.

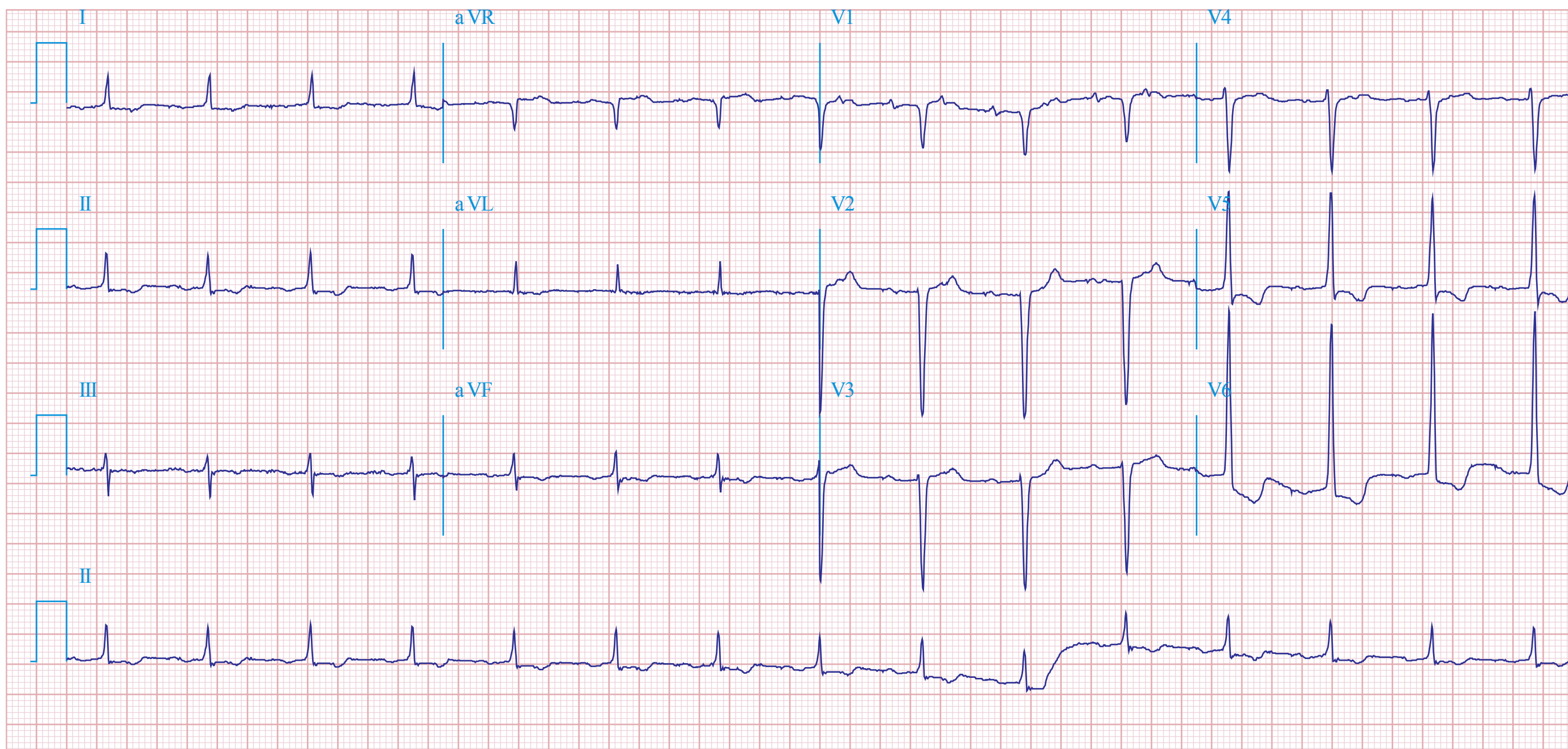


FIGURE 52-12

Atrial tachycardia (180/min with 2:1 AV block [see lead V₁]). LVH by precordial voltage and nonspecific ST-T changes. Slow R-wave progression (V₁–V₄) raises consideration of prior anterior MI.

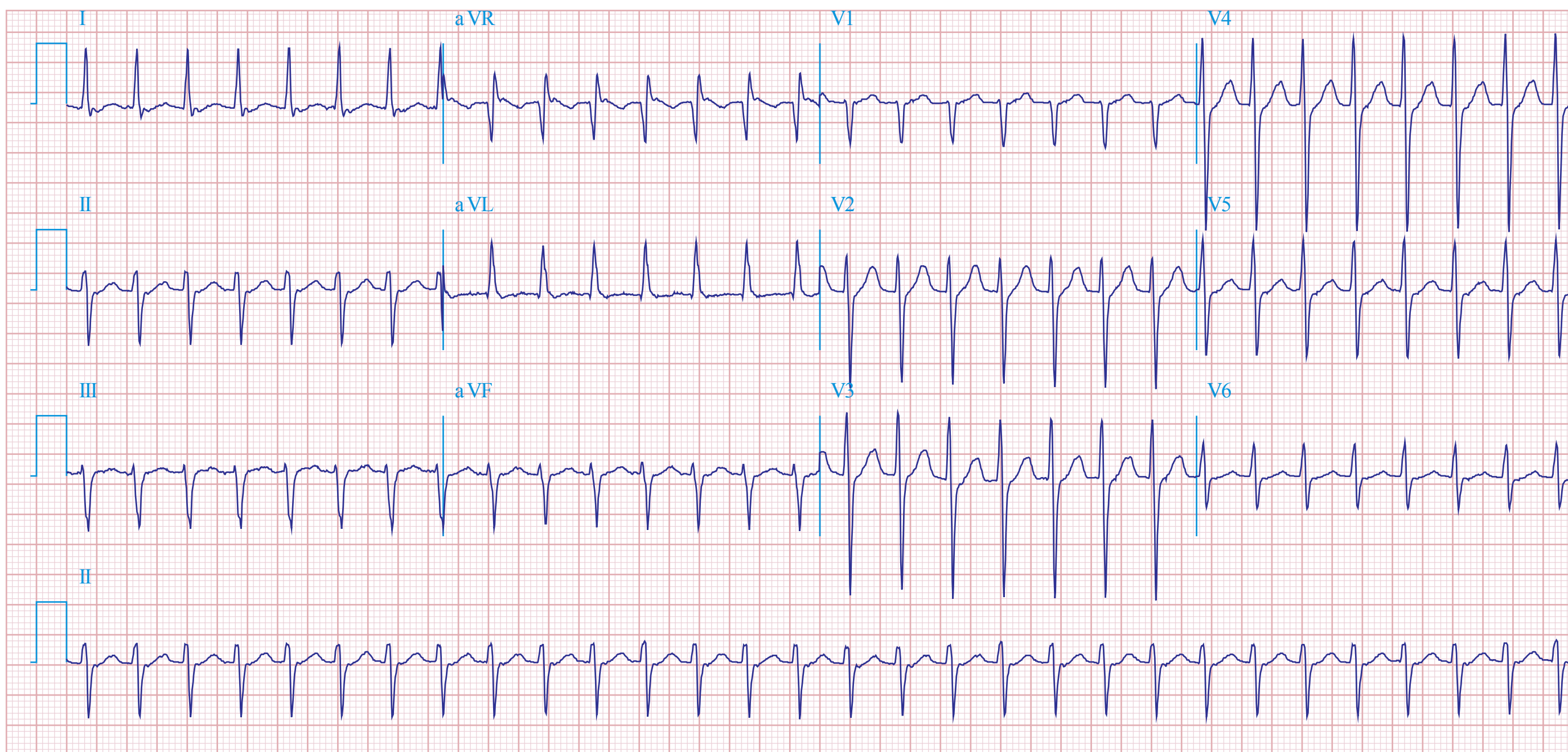


FIGURE 52-13

AV nodal reentrant tachycardia (AVNRT) at a rate of 150/min. Note subtle “pseudo” R waves in lead aVR due to retrograde atrial activation, which usually occurs nearly simultaneous

with ventricles in AVNRT. Left-axis deviation consistent with left anterior fascicular block (hemiblock) is also present.

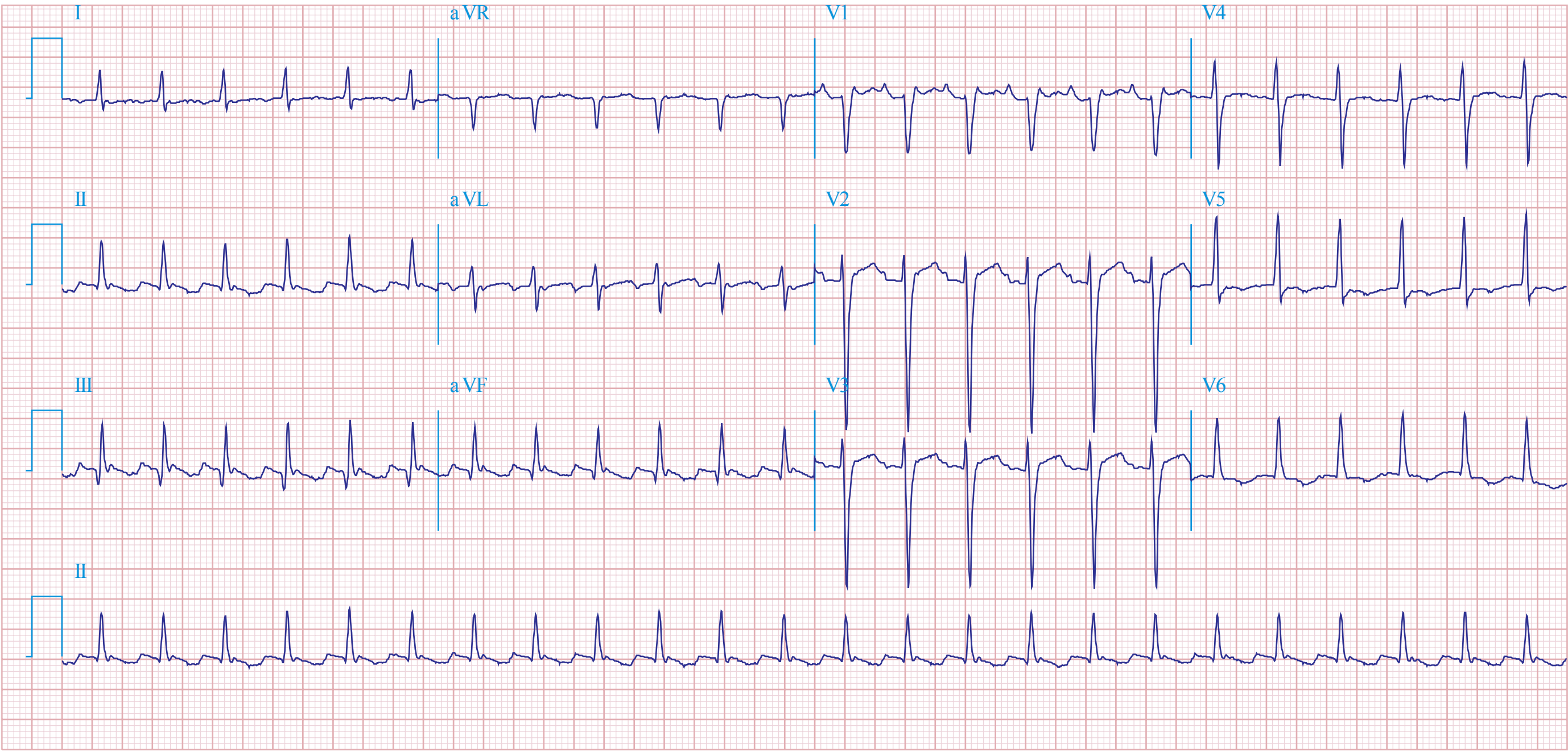


FIGURE 52-14
Atrial flutter with 2:1 AV conduction. Note typical atrial flutter waves, partly hidden in the early ST segment, seen, for example, in leads II and V₁.

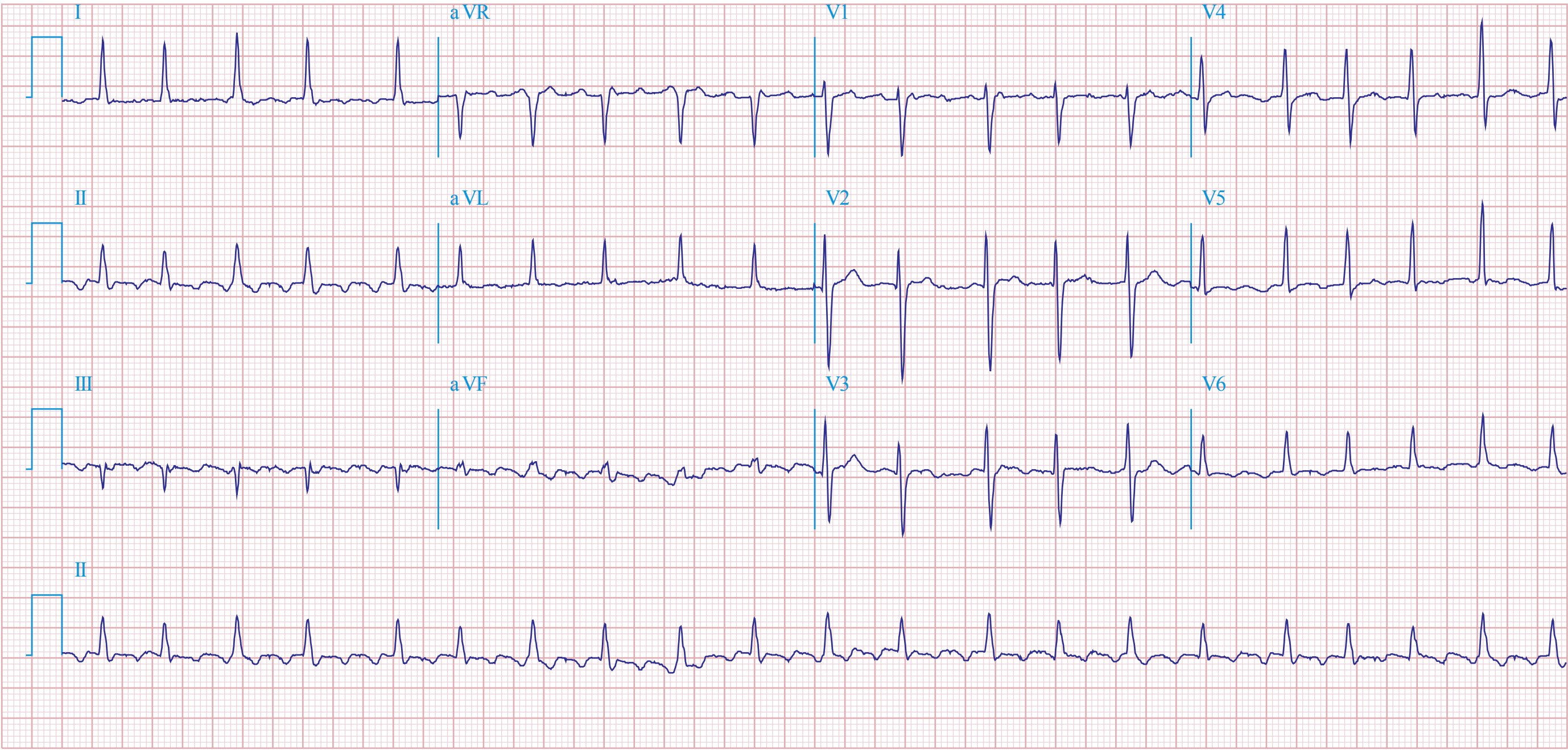


FIGURE 52-15
Atrial flutter with atrial rate 300/min and variable (predominant 2:1 and 3:1) AV conduction. Typical flutter waves are best seen in lead II.

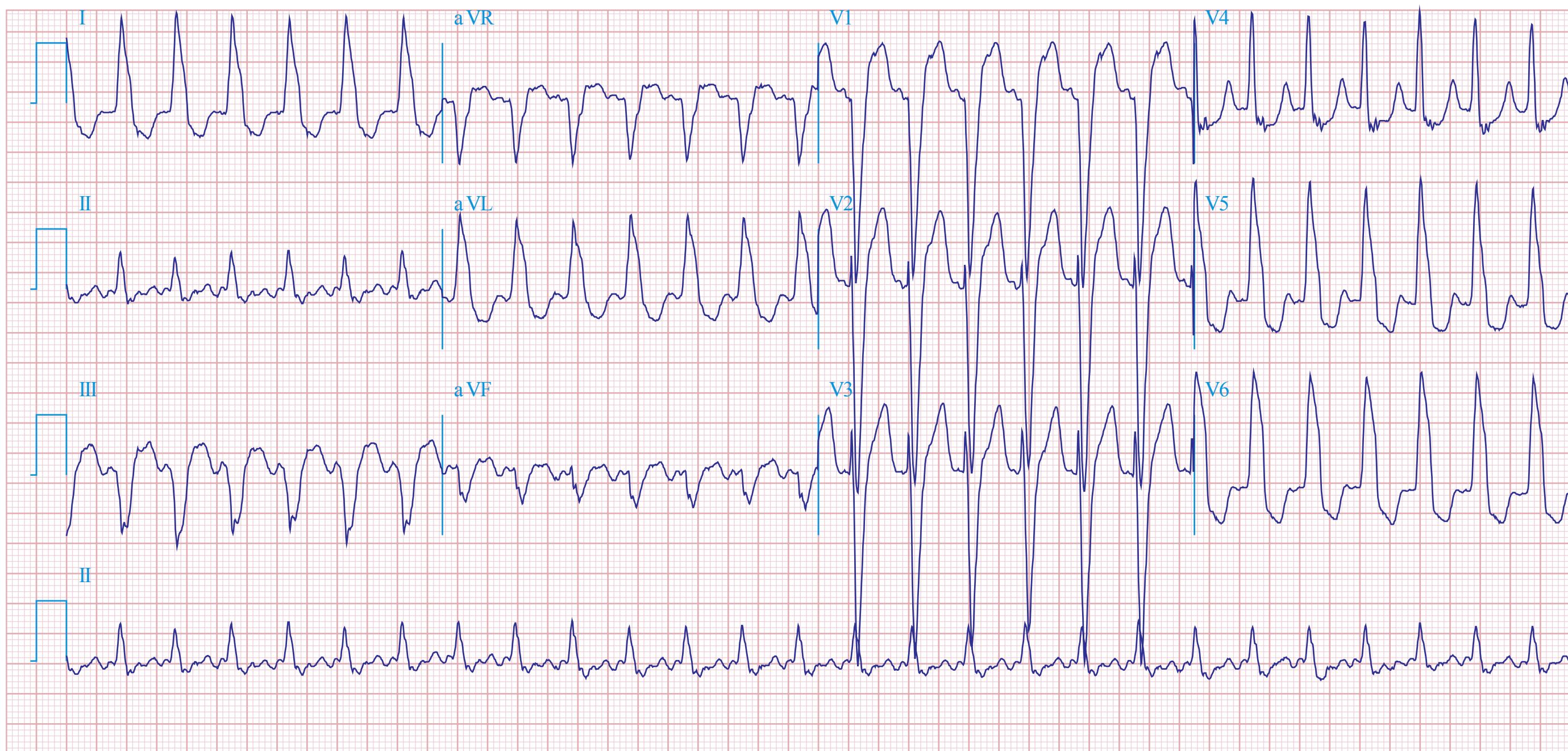


FIGURE 52-16

Wide complex tachycardia. Atrial flutter with 2:1 AV conduction (block) and LBBB, not to be mistaken for VT. Typical atrial flutter activity is clearly present in lead II, at a cycle rate of about 320/min, yielding an effective ventricular rate of about 160/min.

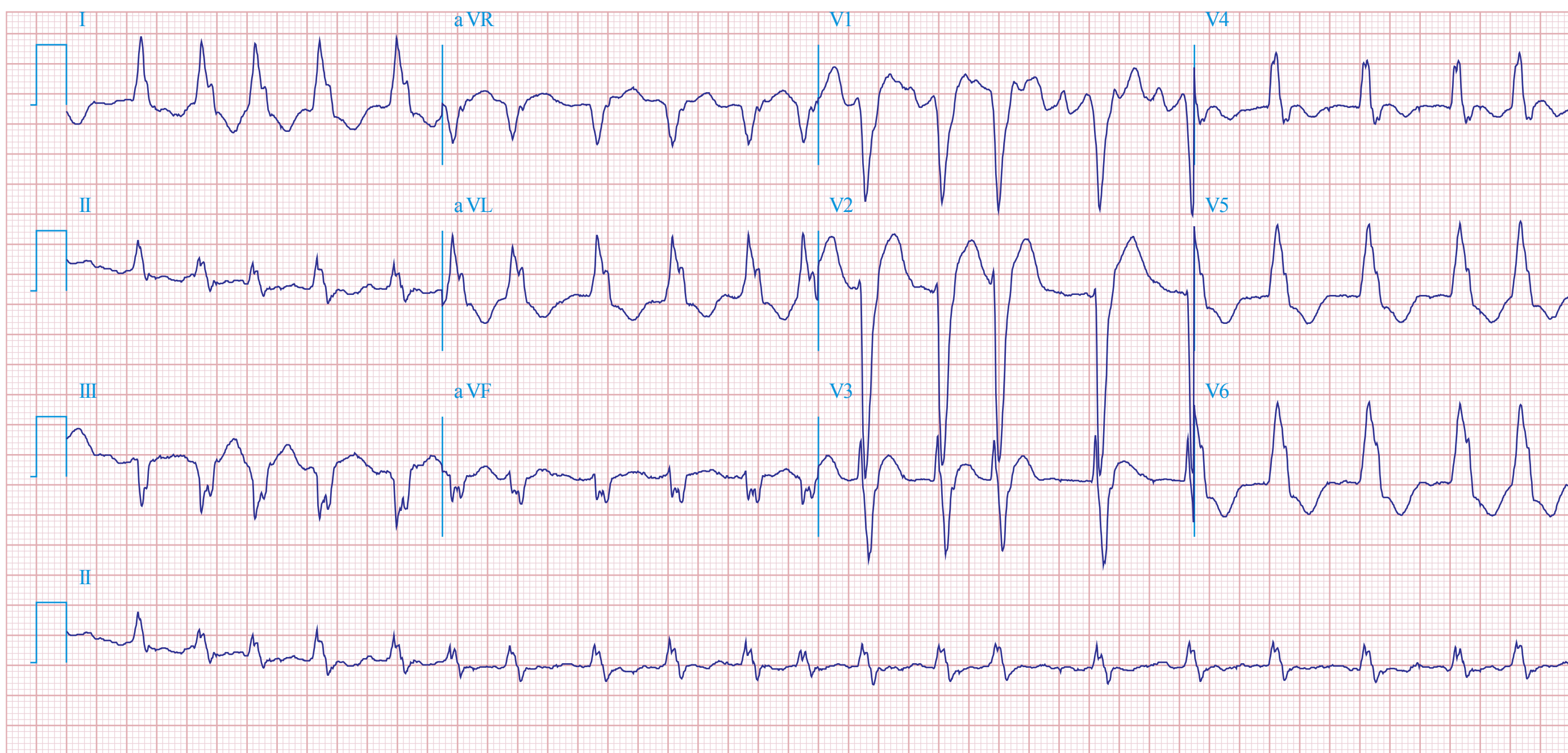


FIGURE 52-17

AF with LBBB. The ventricular rhythm is erratically irregular. Coarse fibrillatory waves are best seen in lead V₁, with a typical LBBB pattern.

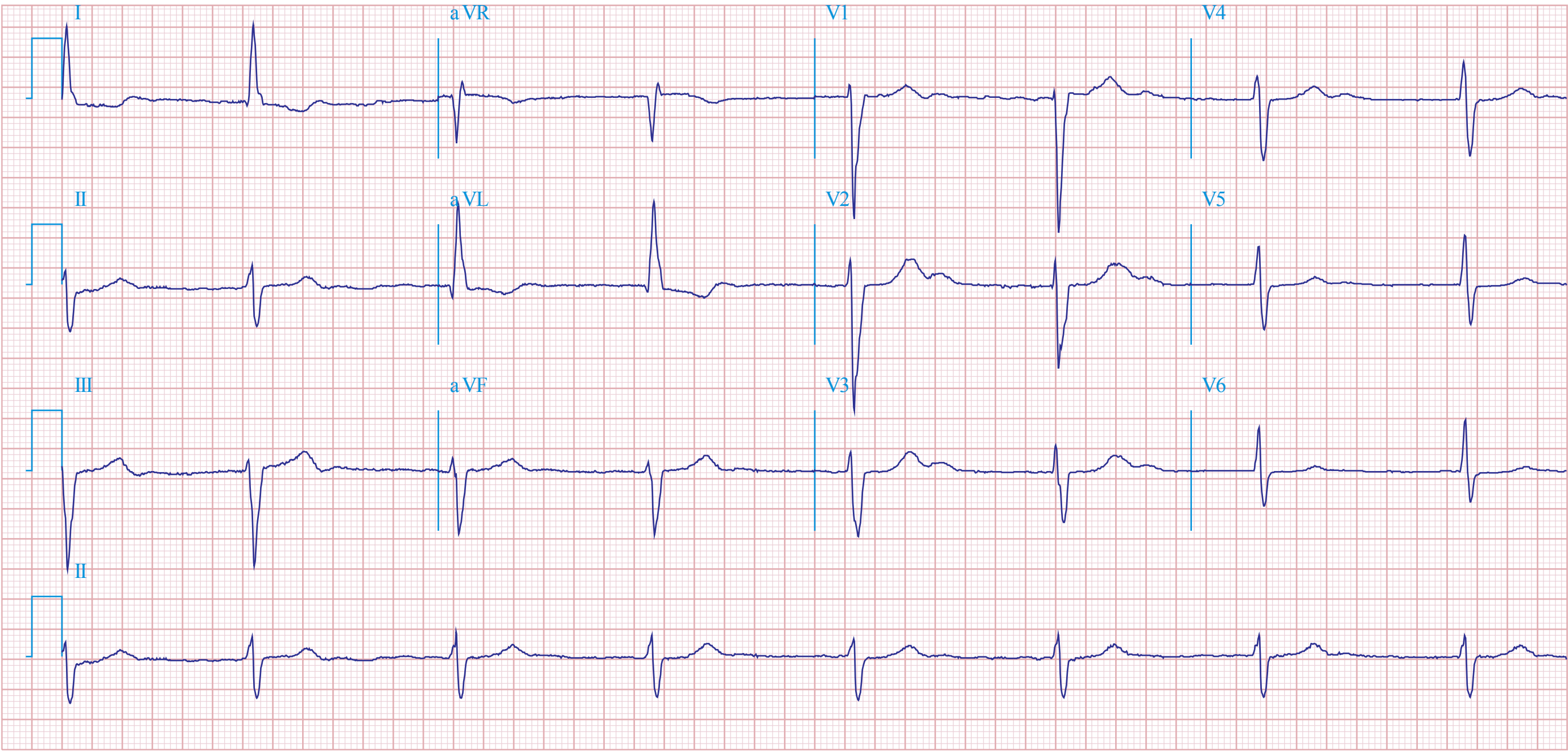


FIGURE 52-18
AF with complete heart block and a junctional escape mechanism causing a slow regular ventricular response (45/min). The QRS complexes show an intraventricular conduction delay with left-axis deviation and LVH. Q-T(U) prolongation is also present.

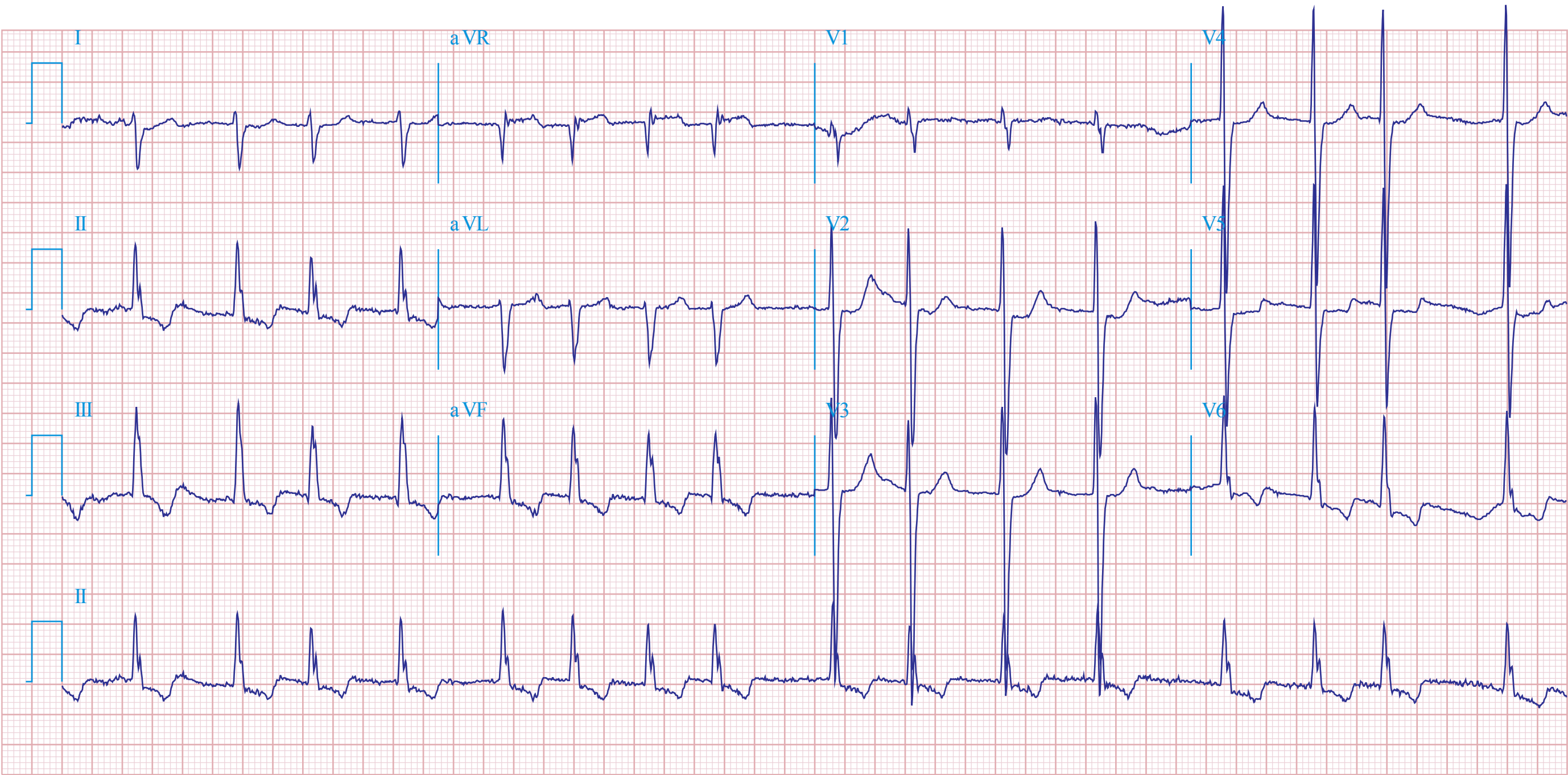


FIGURE 52-19
AF with right-axis deviation and LVH. Tracing suggests biventricular hypertrophy in a patient with mitral stenosis and aortic valve disease.

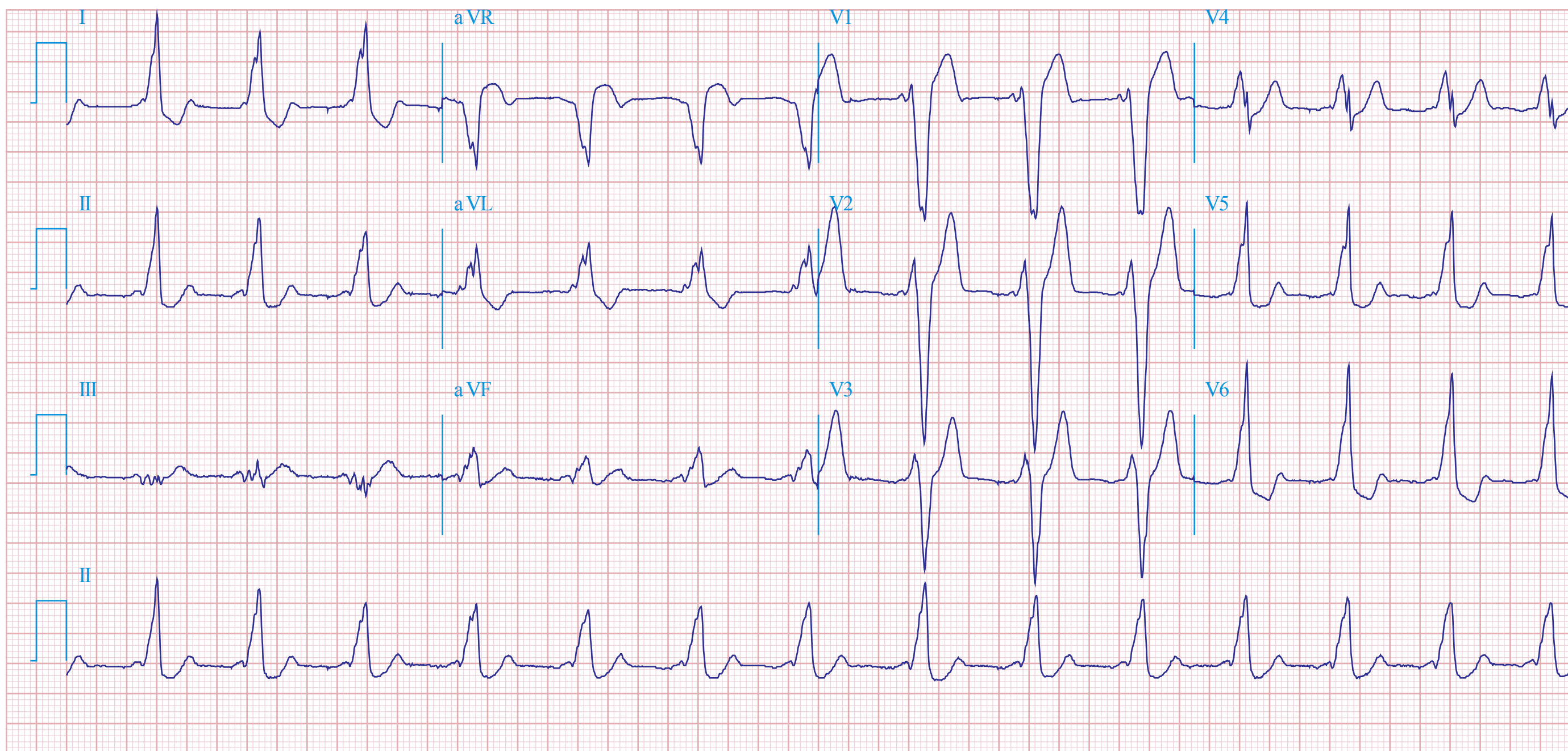


FIGURE 52-20

WPW preexcitation pattern, with triad of short PR, wide QRS, and delta waves. Polarity of the delta waves (slightly positive in leads V_1 and V_2 and most positive in lead II and lateral chest leads) is consistent with a right-sided bypass tract.

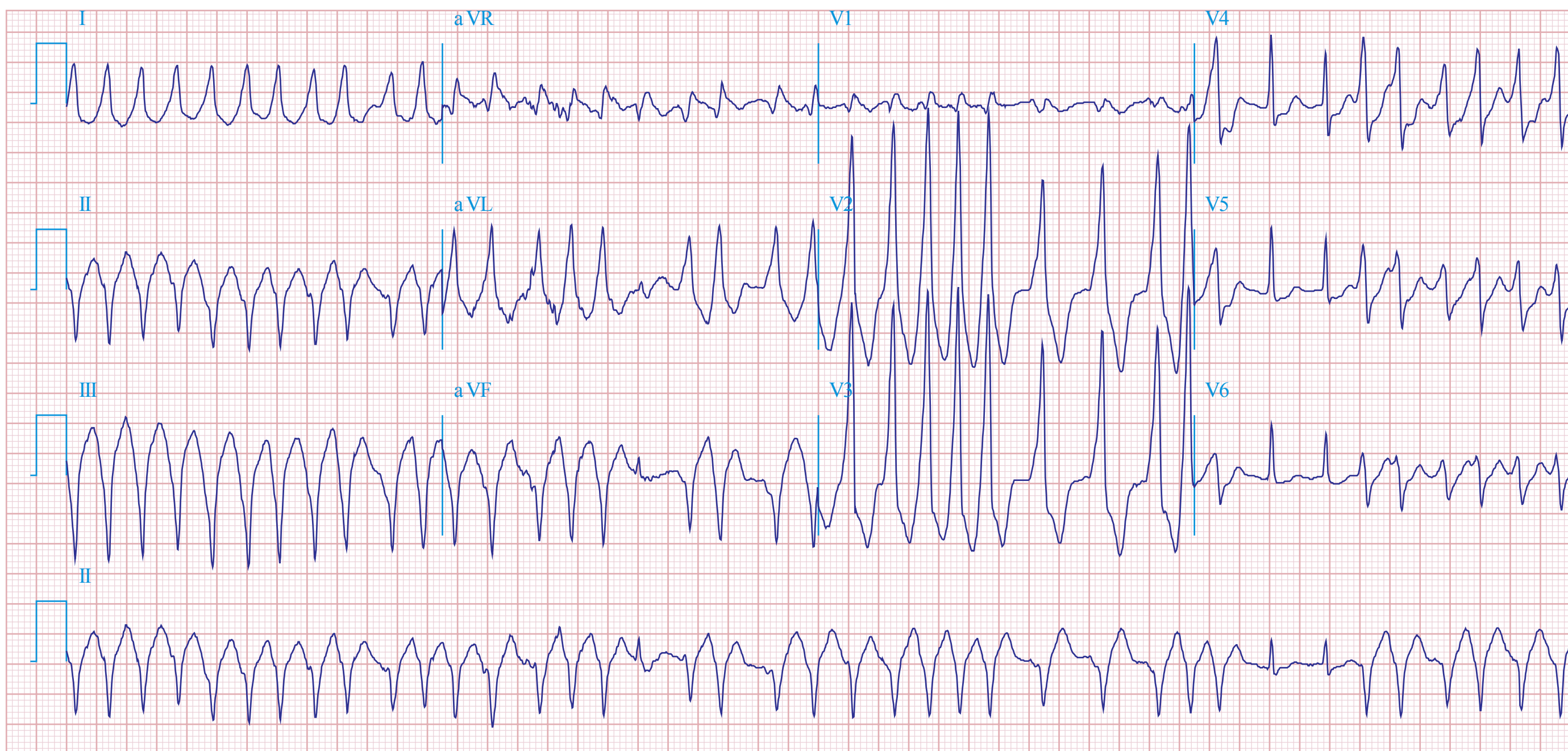


FIGURE 52-21

AF in patient with the WPW syndrome and antegrade conduction down the bypass tract leading to a wide complex tachycardia. Rhythm is “irregularly irregular,” and rate is extremely rapid (about 230/min). Not all beats are preexcited.

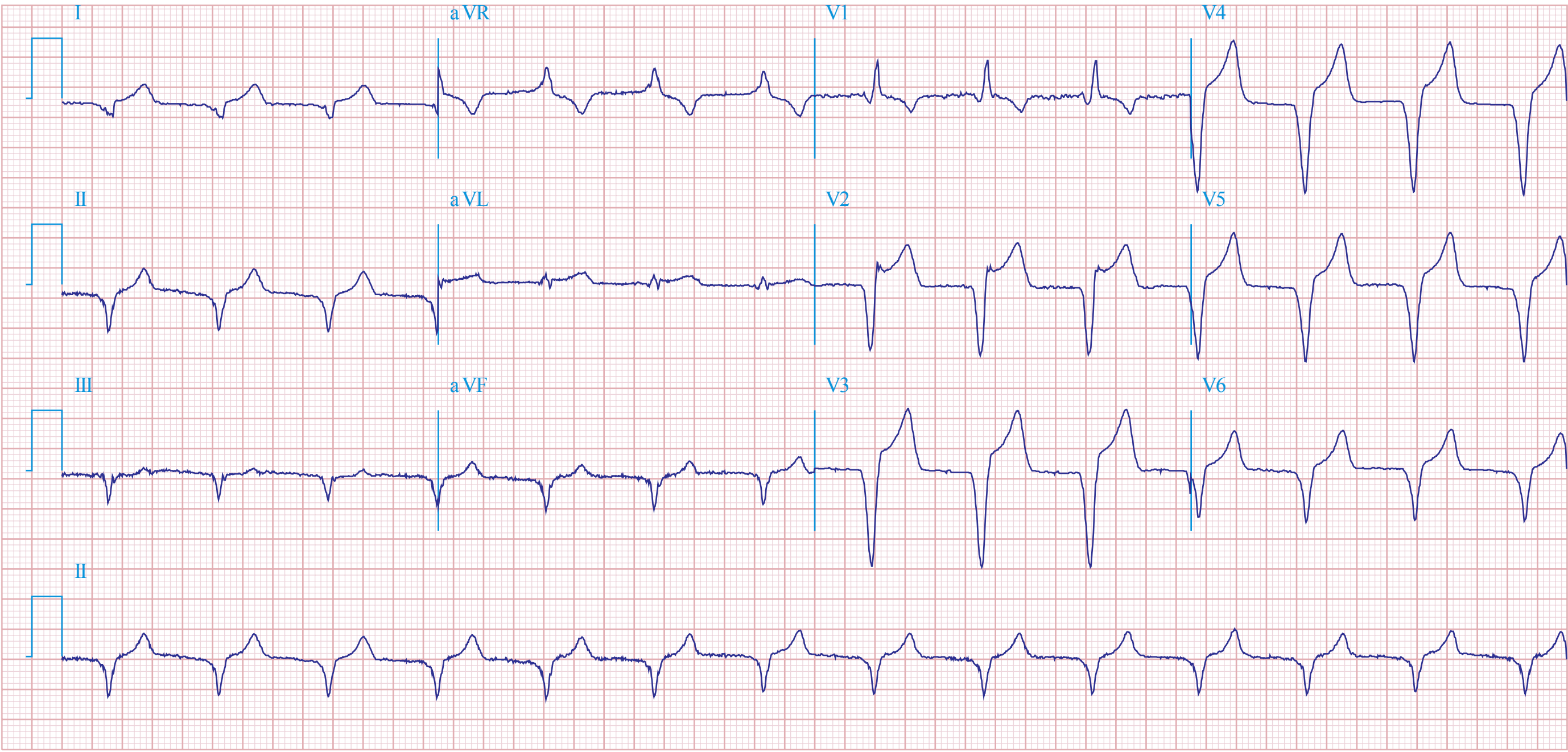


FIGURE 52-22
Accelerated idioventricular rhythm (AIVR) originating from the LV and accounting for RBBB morphology. ST elevations in the precordial leads from underlying acute MI.

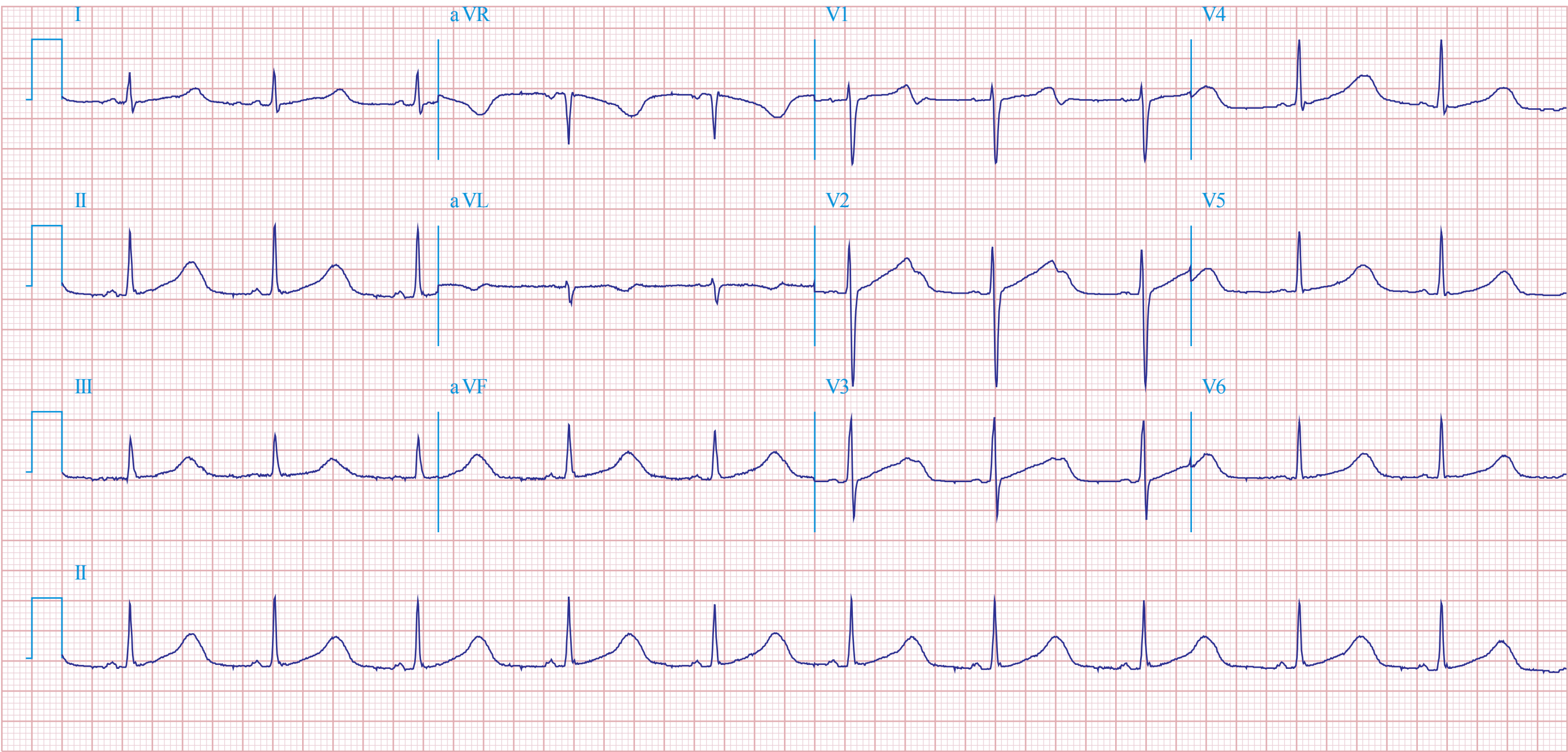


FIGURE 52-23
Prolonged (0.60 s) QT interval in a patient with a hereditary long QT syndrome.

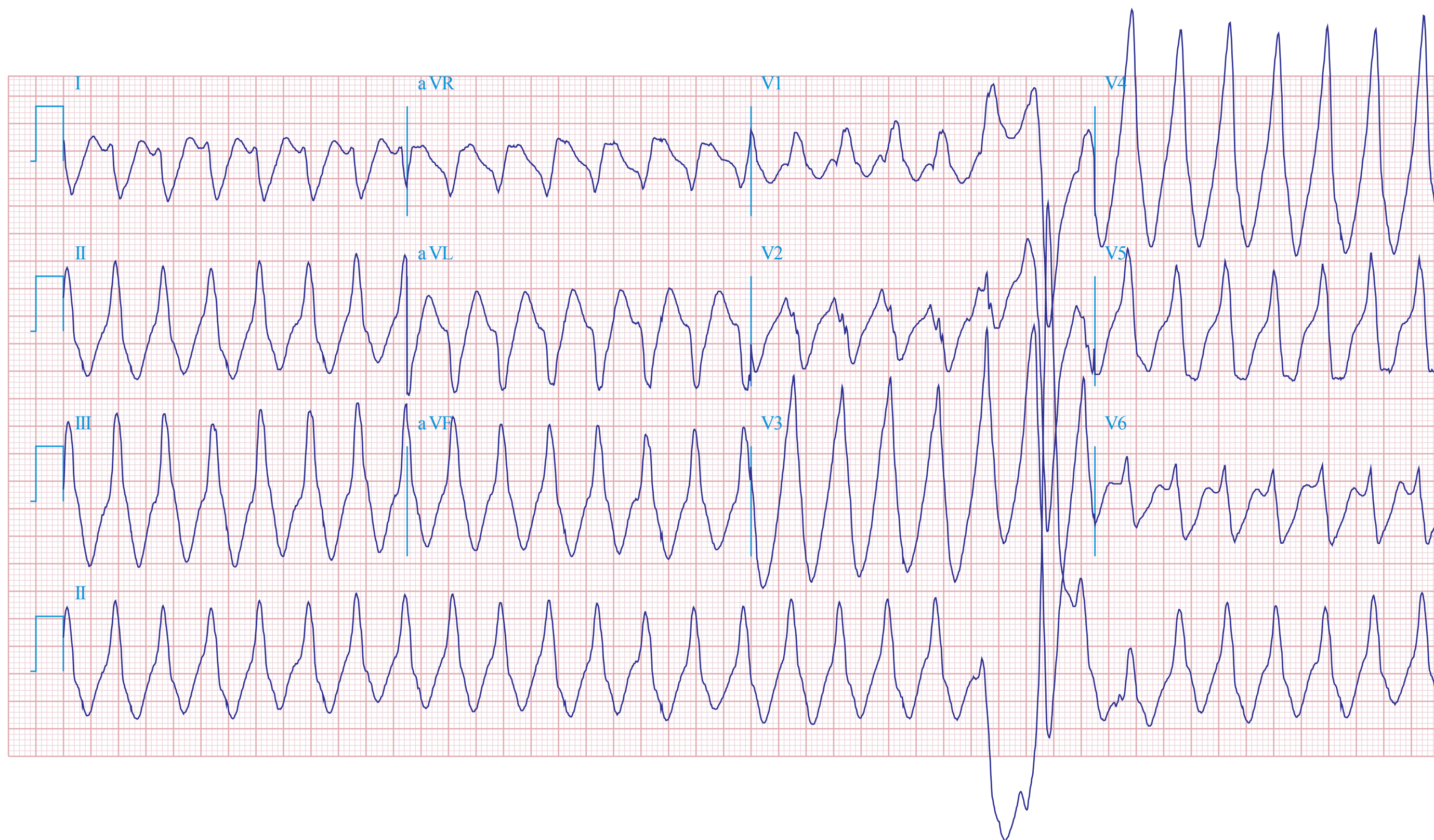


FIGURE 52-24

Monomorphic VT at rate of 170/min. The RBBB morphology in V_1 and the R/S ratio <1 in V_6 are both suggestive of VT. The morphology of the VT is suggestive of origin from the left side of the heart, near the base (RBBB with inferior/rightward axis). Baseline artifact is present in leads V_1 – V_3 .

CHAPTER 53

ATLAS OF PERCUTANEOUS REVASCULARIZATION



Jane A. Leopold ■ Deepak L. Bhatt ■ David P. Faxon

Percutaneous coronary intervention (PCI) is the most widely employed coronary revascularization procedure worldwide (**Chap. 42**). It is now applied to patients with stable angina; patients with acute coronary syndromes, including unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI); and as a primary treatment strategy in patients with ST-segment elevation myocardial infarction (STEMI). PCI is also applicable to patients with either single-vessel or multivessel disease.

In this chapter, the use of PCI will be illustrated in a variety of commonly encountered clinical and anatomic situations, such as chronic total occlusion of a coronary artery, bifurcation disease, acute STEMI, saphenous vein graft disease, left main coronary artery disease, multivessel disease, and stent thrombosis. In addition, the use of interventional techniques to treat structural heart disease will be shown, including closure of an atrial septal defect (ASD) and transcatheter aortic valve replacement (TAVR).

CASE 1: CHRONIC TOTAL OCCLUSION

(**Videos 53-1, 53-2, 53-3, 53-4, 53-5, 53-6, and 53-7**)

- An 81-year-old male with angina, New York Heart Association (NYHA) class IV congestive heart failure and inferoapicoposterior ischemia on an exercise technetium-99m scan.
- Diagnostic cardiac catheterization revealed a left dominant system with a totally occluded left circumflex (LCx) artery. The distal LCx filled via collaterals from the left anterior descending (LAD) artery, indicating chronicity of the total occlusion.

SUMMARY

- Approximately 15–30% of all patients referred for cardiac catheterization will have a chronic total occlusion (CTO) of a coronary artery.

- CTO often leads to a surgical referral for complete revascularization.
- Incomplete revascularization due to an untreated CTO is associated with an increased mortality rate (hazard ratio = 1.36; 95% confidence interval [CI], 1.12–1.66, $p < .05$).
- Successful PCI of a CTO leads to a 3.8–8.4% absolute reduction in mortality, symptom relief, and improved left ventricular function.
- Newer techniques, such as the retrograde approach to crossing total occlusions, are useful when the antegrade approach fails or is not feasible and there are well-developed collateral vessels.

(Case contributed with permission by Dr. Frederick G.P. Welt.)

CASE 2: BIFURCATION STENTING

(**Fig. 53-1; Videos 53-8, 53-9, 53-10, 53-11, 53-12, 53-13, 53-14, 53-15, and 53-16**)

- A 52-year-old male with an acute coronary syndrome and a troponin I = 0.18 (upper limit of normal, <0.04).
- Diagnostic cardiac catheterization showed single-vessel coronary artery disease with a significant stenosis in the mid-LAD and a bifurcation lesion involving a large diagonal branch.

SUMMARY

- Approximately 15–20% of PCIs will involve the treatment of bifurcation lesions.
- Bifurcation lesions require consideration of PCI strategies that protect side-branch patency.
- There are both one-stent and two-stent techniques to treat bifurcation lesions; the selection of technique depends on anatomic considerations, including plaque burden, angle of side-branch take-off,

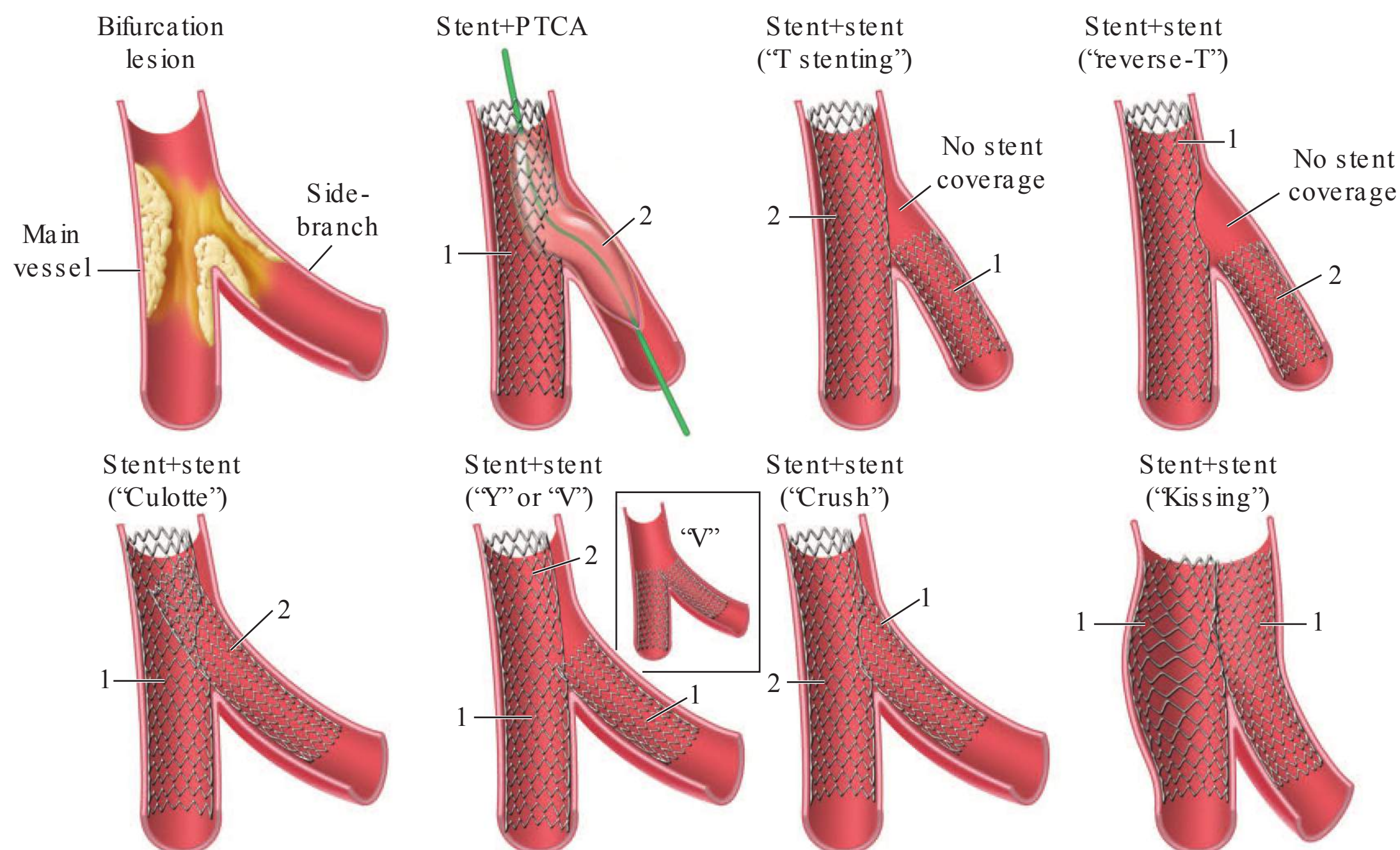


FIGURE 53-1

Schematic representation of one-stent and two-stent techniques to treat bifurcation lesions. PTCA, percutaneous transluminal coronary angioplasty

plaque shift during angioplasty, and side-branch distribution.

- Rates of target lesion revascularization and stent thrombosis are similar between one-stent and two-stent procedures.

CASE 3: INFERIOR MYOCARDIAL INFARCTION—THROMBUS AND MANUAL THROMBECTOMY

(Figs. 53-2 to 53-4; Videos 53-17 to 53-22)

- A 59-year-old male presented to the emergency room with 2 h of severe midsternal chest pressure.
- His systolic blood pressure was 100 mmHg, and he was tachycardic in sinus rhythm with a heart rate of 90–100 beats/min.
- His initial electrocardiogram (ECG) showed inferior ST-segment elevations with lateral ST-segment depressions.
- He was referred emergently to the cardiac catheterization laboratory for primary PCI.

SUMMARY

- An acute STEMI occurs following plaque rupture that promotes thrombotic occlusion of a coronary artery.

- Despite successful revascularization of the epicardial coronary artery, microemboli liberated during balloon angioplasty and stenting may lead to persistent microvascular dysfunction. When present, microvascular dysfunction is associated with a larger infarct size, heart failure, malignant ventricular arrhythmias, and death.

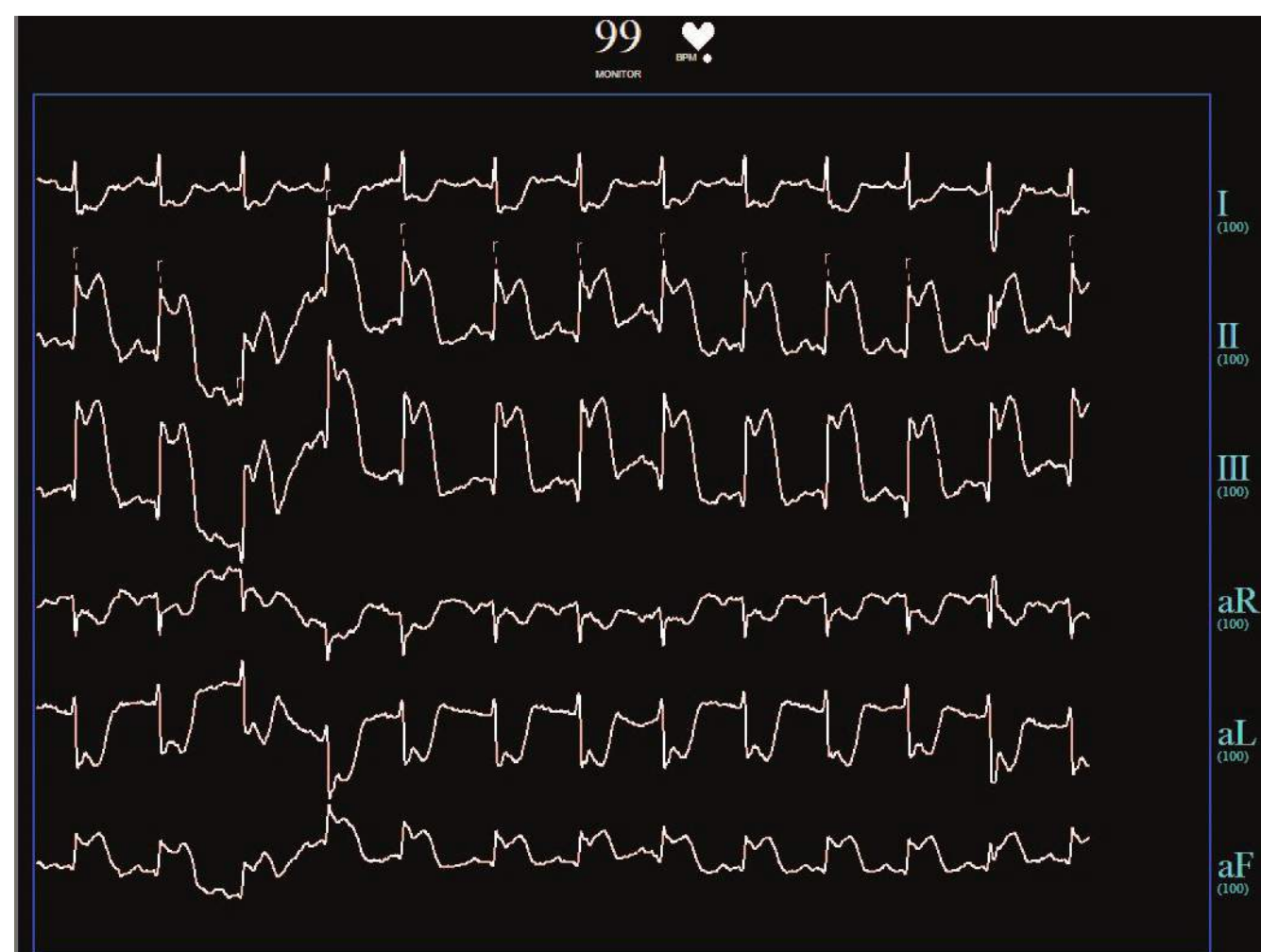


FIGURE 53-2

Preprocedure ECG showing inferior ST-segment elevations and lateral ST-segment depressions.

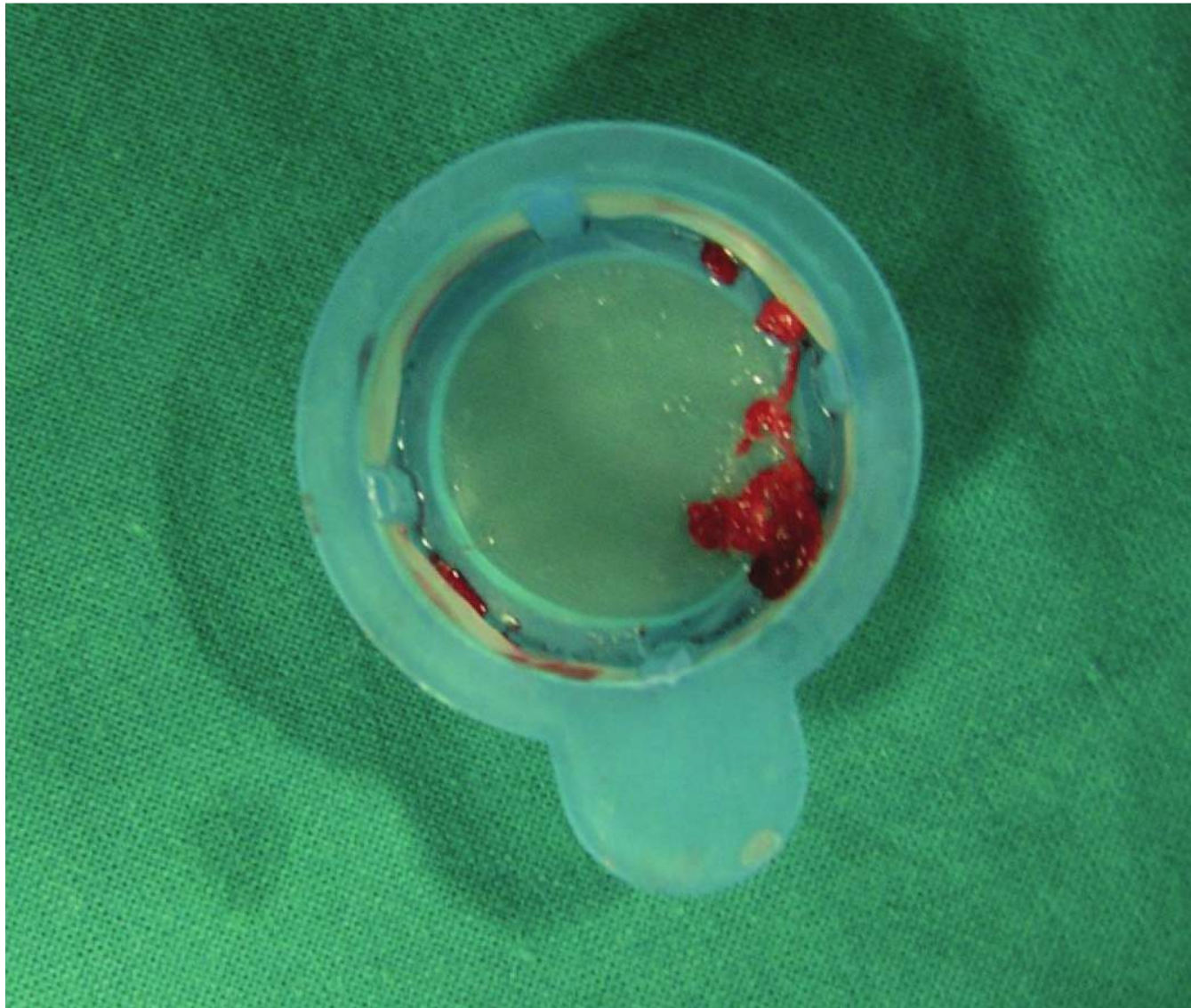


FIGURE 53-3

Example of an organized red thrombus retrieved by manual thrombectomy.

- Manual thrombectomy is used to aspirate or remove thrombus in the vessel and limit distal embolization during angioplasty and stenting.
- Manual thrombectomy in primary PCI is associated with improved myocardial perfusion and a reduction in mortality.
- Adjunctive antiplatelet and antithrombin agents are important to aid in the resolution of intracoronary thrombus.

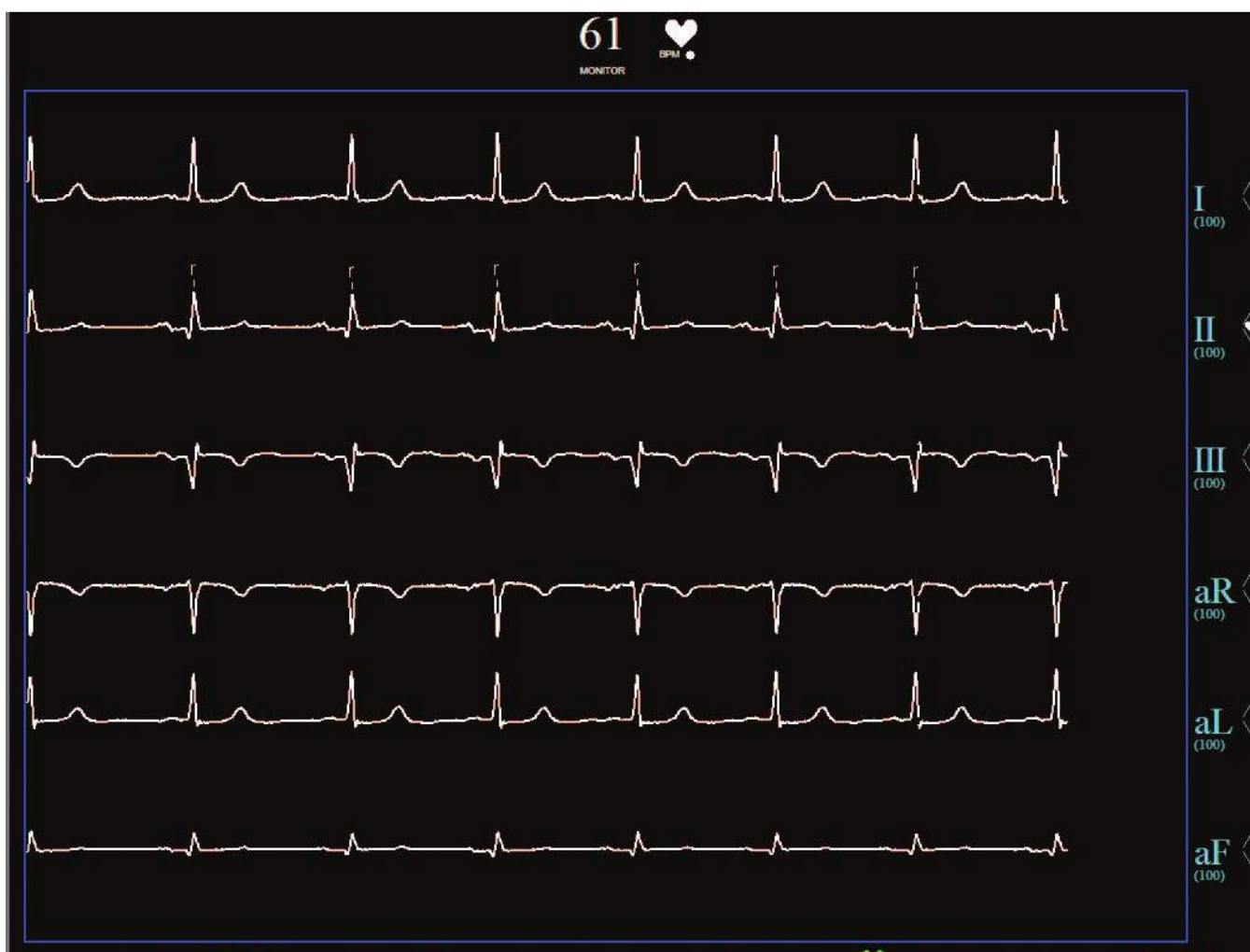


FIGURE 53-4

Postprocedural ECG showing resolution of ST-segment elevations.

CASE 4: SAPHENOUS VEIN GRAFT INTERVENTION WITH DISTAL PROTECTION

(Fig. 53-5; Videos 53-23 to 53-26)

- A 62-year-old male with a history of chronic stable angina.
- A four-vessel coronary artery bypass grafting (CABG) surgery was performed 17 years earlier with a left internal mammary artery graft to the LAD, a right internal mammary artery graft to the right coronary artery (RCA), a saphenous vein graft to the first obtuse marginal branch, and a saphenous vein graft to the first diagonal branch.
- The patient had a recent increase in angina with exertion and was found to have lateral ischemia on an exercise technetium-99m scan.
- Diagnostic cardiac catheterization revealed a significant stenosis in the body of the saphenous vein graft to the first obtuse marginal branch.

SUMMARY

- Saphenous vein grafts have a failure rate of up to 20% after 1 year and as high as 50% by 5 years.
- Graft failure (after >1 month) results from intimal hyperplasia and atherosclerosis.
- Saphenous vein graft PCI is associated with distal embolization of atherosclerotic debris and microthrombi leading to microvascular occlusion, reduced antegrade blood flow (the “no-reflow” phenomenon), and myocardial infarction.
- Embolic distal protection devices decrease the risk of distal embolization, as well as the incidence of no-reflow and myocardial infarction associated with saphenous vein graft interventions.



FIGURE 53-5

Distal protection device showing captured atherosclerotic debris liberated by initial balloon dilation.

CASE 5: UNPROTECTED LEFT MAIN PCI IN A HIGH-RISK PATIENT

(Figs. 53-6 and 53-7; Videos 53-27 to 53-34)

- An 89-year-old woman presented with a NSTEMI associated with 5-mm ST-segment depression in the apical leads occurring 2 weeks after hospitalization for a NSTEMI that was treated conservatively.
- Chronic obstructive lung disease, elderly age, and the patient's refusal to consider cardiac surgery restricted the choice of therapeutic options to medical and/or percutaneous interventions.
- Diagnostic catheterization revealed a left dominant circulation with a heavily calcified 80% distal left main coronary artery stenosis extending into the LAD and into the proximal LCx coronary arteries. A 70% proximal LAD lesion was also present.

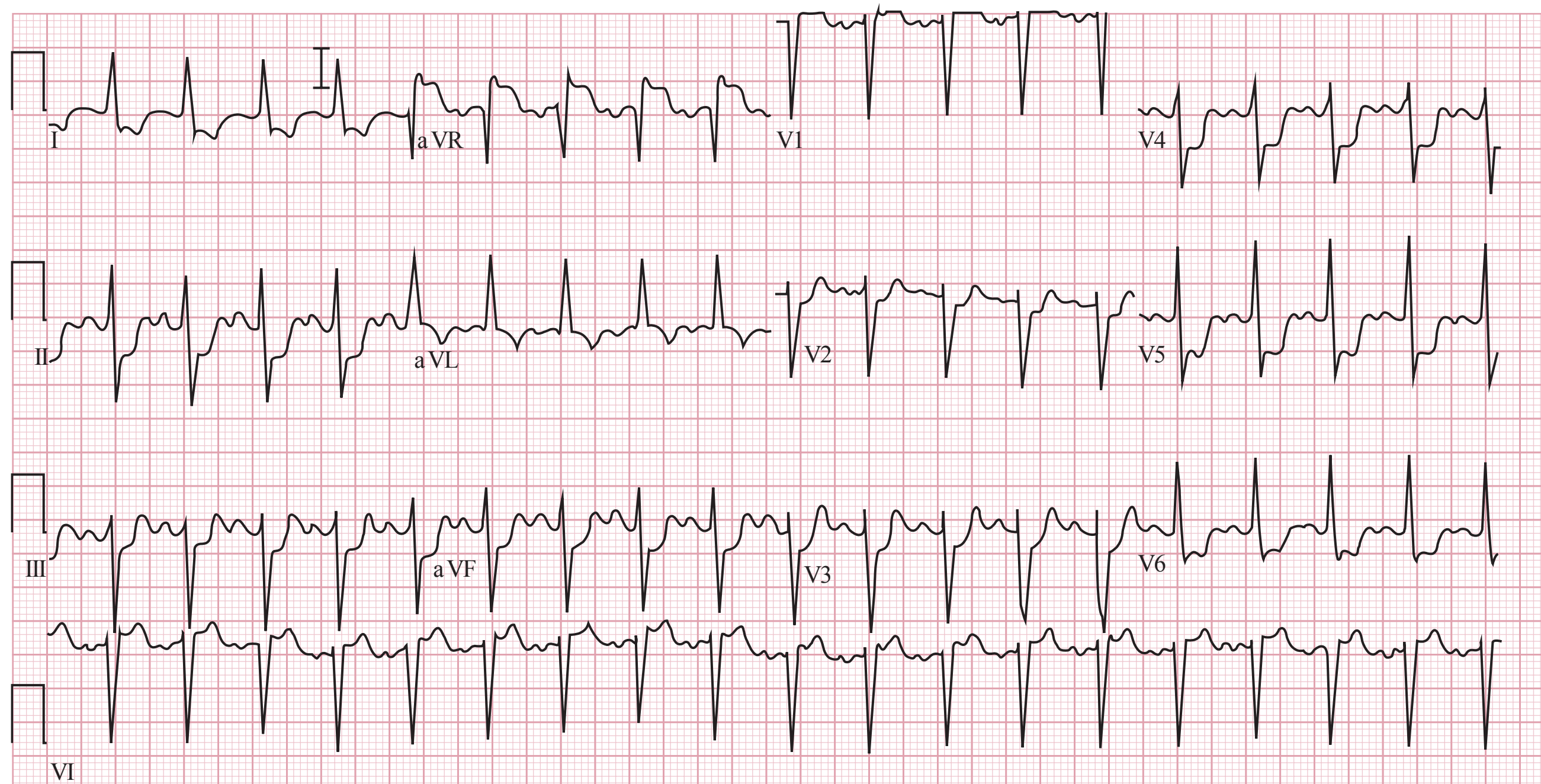


FIGURE 53-6

During chest pain, the ECG showed diffuse ST-segment depression of up to 5 mm in the inferior and lateral leads.

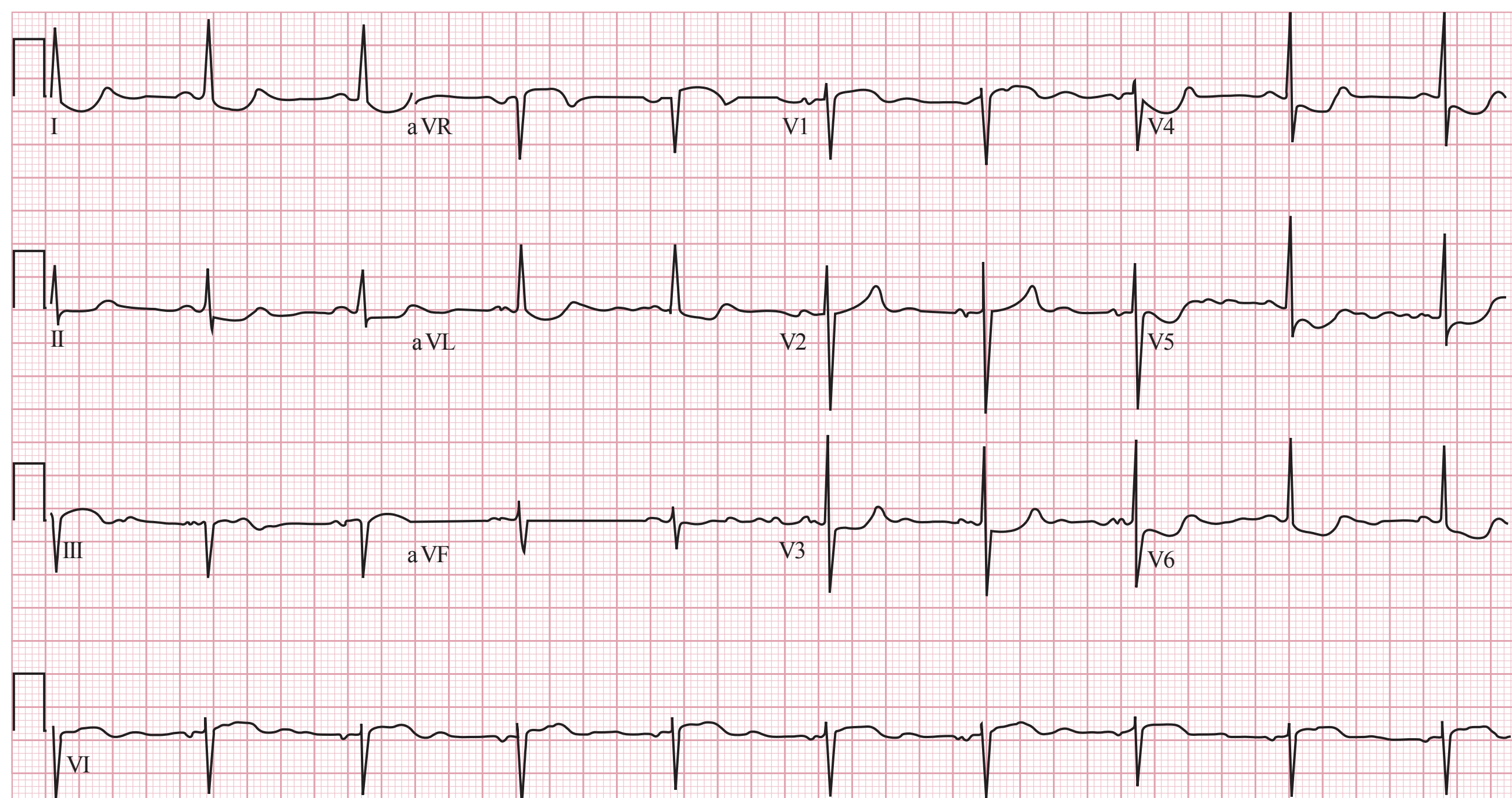


FIGURE 53-7

Following resolution of the chest pain, the ST-segment depression is less marked.

- After consultation with the patient, family, and a cardiac surgeon, PCI was performed with intraaortic balloon pump support and a temporary pacemaker in the right ventricle.

SUMMARY

- Left main coronary artery disease occurs in 5–10% of patients with symptomatic coronary artery disease.
- In patients with left main coronary artery disease, revascularization with CABG has been shown to decrease mortality significantly over 5–10 years of follow-up.
- PCI with drug-eluting stents in selected cases has been shown to have equal in-hospital and 1-year death and myocardial infarction rates compared with CABG in the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial. Long-term outcome differences between the two treatment strategies are not known.
- Indications for PCI of left main coronary artery lesions are high-risk surgical patients and patients with protected left main coronary artery disease (i.e., prior CABG with patent bypass grafts). Patients who are good candidates for bypass surgery may also undergo a stenting procedure, but discussion with the patient, the interventional cardiologist, and the cardiac surgeon should be undertaken to determine the best treatment option in an individual case.
- Outcomes are better for patients with an isolated lesion in the ostium and body of the left main coronary artery where a single stent can be placed compared to bifurcation lesions that involve the ostium of the LAD and LCx.

CASE 6: MULTIVESSEL PCI IN A DIABETIC PATIENT

(Videos 53-35 to 53-42)

- A 58-year-old man presented with a NSTEMI.
- The patient has hyperlipidemia and type 2 diabetes mellitus treated with oral hypoglycemic agents.
- Diagnostic catheterization revealed two-vessel disease with a total occlusion of the second obtuse marginal branch that was felt to be responsible for the patient's symptoms (culprit lesion). In addition, there was a high-grade stenosis in a large ramus intermedius branch, and the RCA had a significant stenosis in the midsegment of the vessel.

SUMMARY

- Multivessel PCI is performed commonly and may be done in one setting or staged with two or more procedures.

- Acute and long-term studies of multivessel PCI have shown comparable rates of death and myocardial infarction when compared to CABG, but a higher incidence of repeat revascularization as a result of restenosis is associated with PCI.
- In the randomized Bypass Angioplasty Revascularization Investigation (BARI) trial, diabetic patients treated with PCI had a worse long-term mortality than diabetic patients treated with CABG. However, the BARI registry found that in selected diabetic patients with favorable anatomy, PCI can result in outcomes equal to those observed with CABG.

CASE 7: VERY LATE STENT THROMBOSIS OF A PROXIMAL LAD DRUG-ELUTING STENT

(Figs. 53-8 and 53-9; Videos 53-43 to 53-46)

- A 62-year-old male had a drug-eluting stent placed in a proximal LAD lesion to treat severe angina. He received dual antiplatelet therapy with aspirin and clopidogrel for 1 year and then discontinued clopidogrel per protocol.
- He remained asymptomatic until 15 months after the initial stent placement when he presented with severe chest pain due to an acute anterior STEMI.

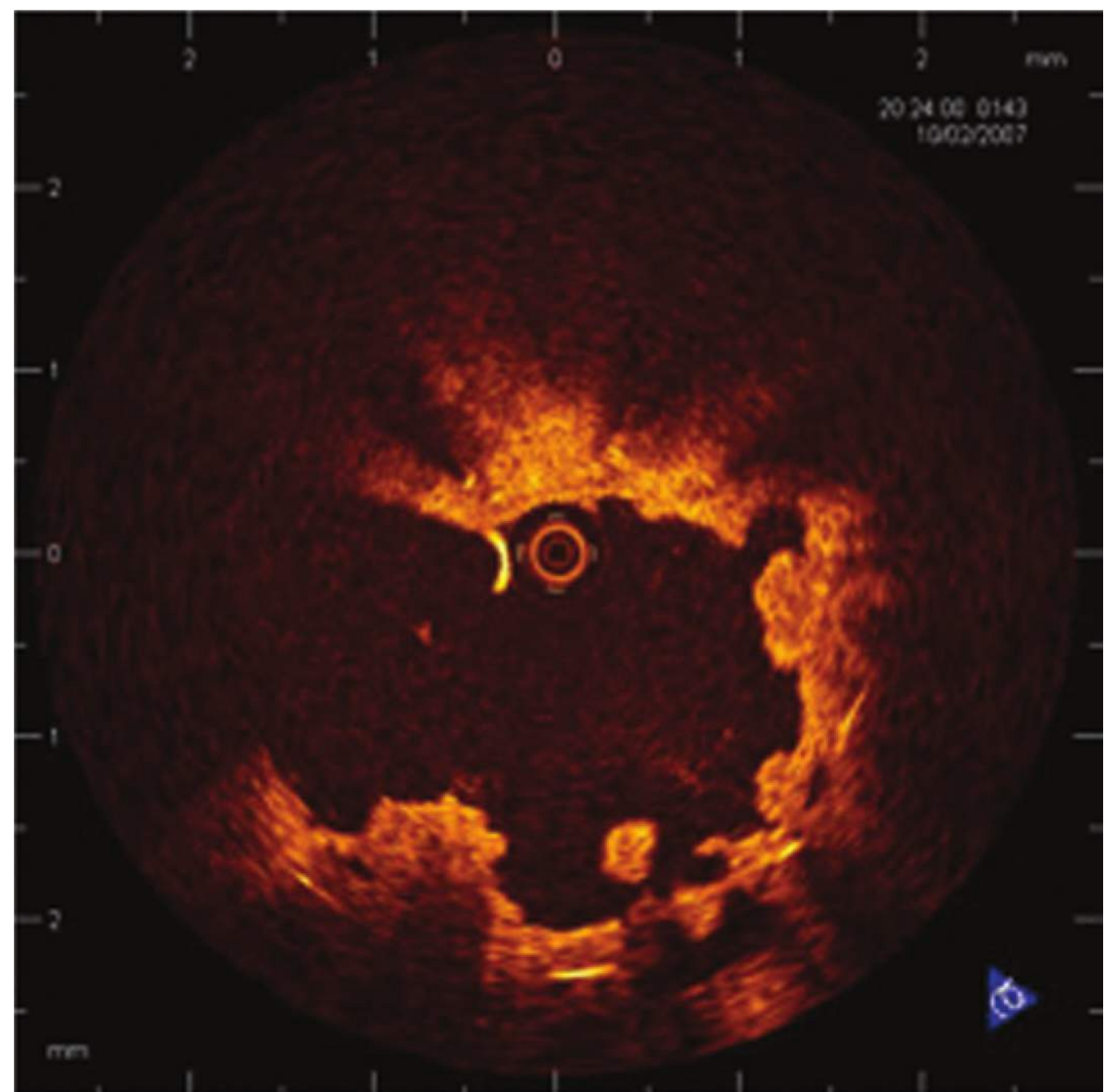


FIGURE 53-8

Optical coherence tomography image following initial balloon dilation. Residual thrombus that is adherent to the stent struts is seen.

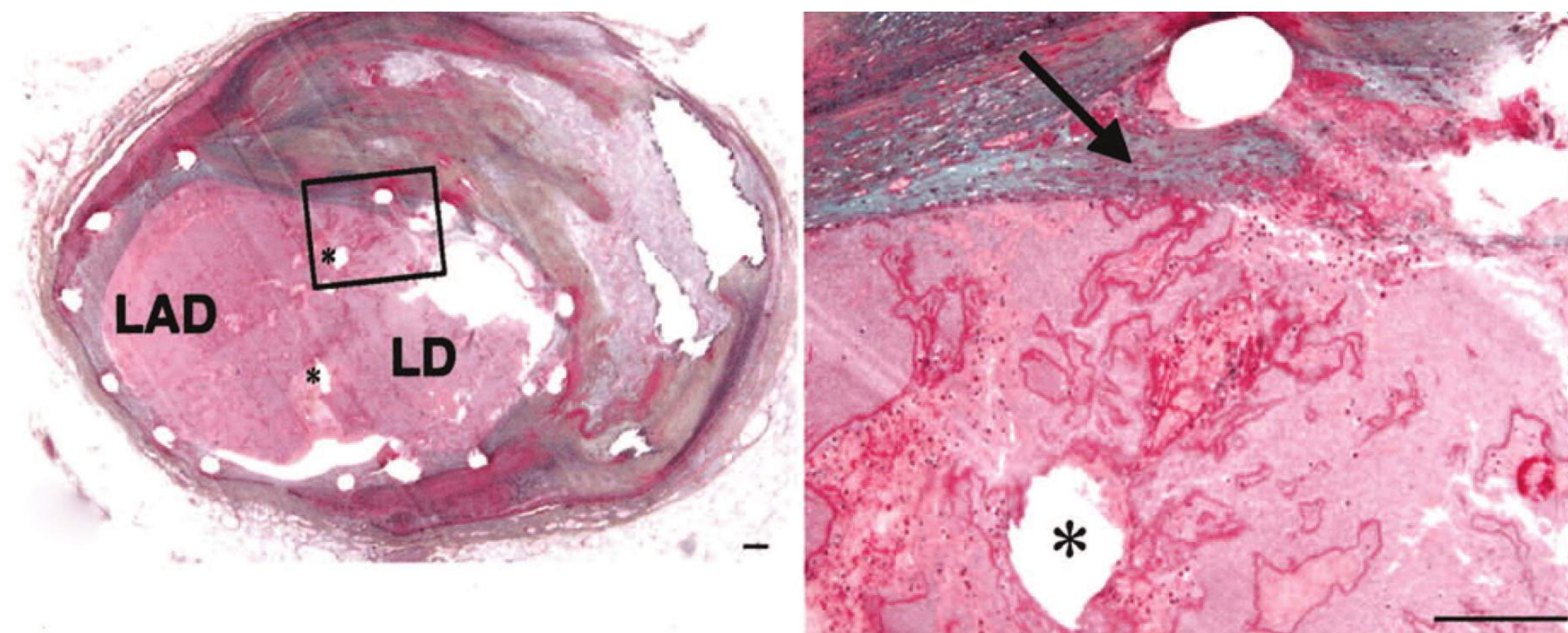


FIGURE 53-9

Pathologic specimen of late stent thrombosis obtained at autopsy. Thrombus is seen filling the LAD vessel lumen and extending into a diagonal branch (LD). Stent struts occupied the

space denoted by the asterisk (*) (left). A magnified view of the vessel reveals thrombus around the stent strut and neointima formation (arrow) (right).

- He was taken to the catheterization laboratory within 70 min of presentation, and his initial angiogram showed a total occlusion of the proximal LAD stent.

SUMMARY

- Stent thrombosis is an infrequent (1–2%) but serious complication of stent placement. It occurs most commonly within the first month, but rarely can occur as late as 1 year (0.2–0.6%) with bare metal stents. Very late stent thrombosis (VLST), which occurs after 1 year, is very rare with bare metal stents but can occur with drug-eluting stents.
- Premature discontinuation of dual antiplatelet therapy is the most common cause of early and late stent thrombosis; however, the etiology of VLST is not clear.
- The majority of patients with stent thrombosis present with acute coronary syndromes or STEMI;

this presentation is associated with a high mortality rate (10%).

- Treatment is immediate PCI with balloon angioplasty or re-stenting.

CASE 8: TRANSCATHETER AORTIC VALVE REPLACEMENT

(Figs. 53-10 to 53-14; Videos 53-47 to 53-50)

- A 75-year-old female with symptomatic aortic stenosis and a valve area of 0.58 cm² by transthoracic echocardiogram.
- Chronic obstructive pulmonary disease (forced expiratory volume in 1 s [FEV₁] = 0.54) and other comorbidities contributed to an unacceptably high cardiac surgical risk (calculated logistic Euroscore = 29.57%) for aortic valve replacement.

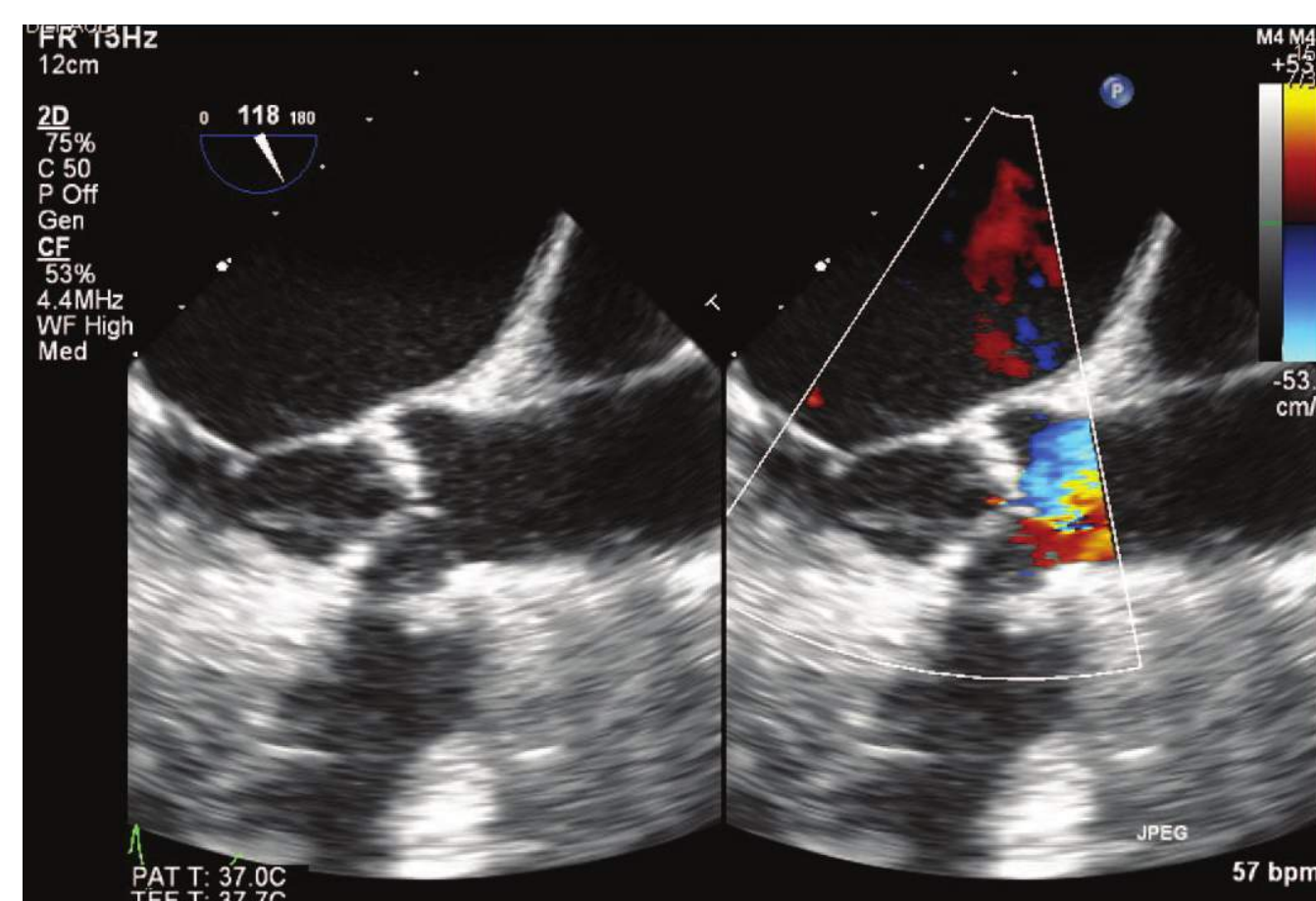
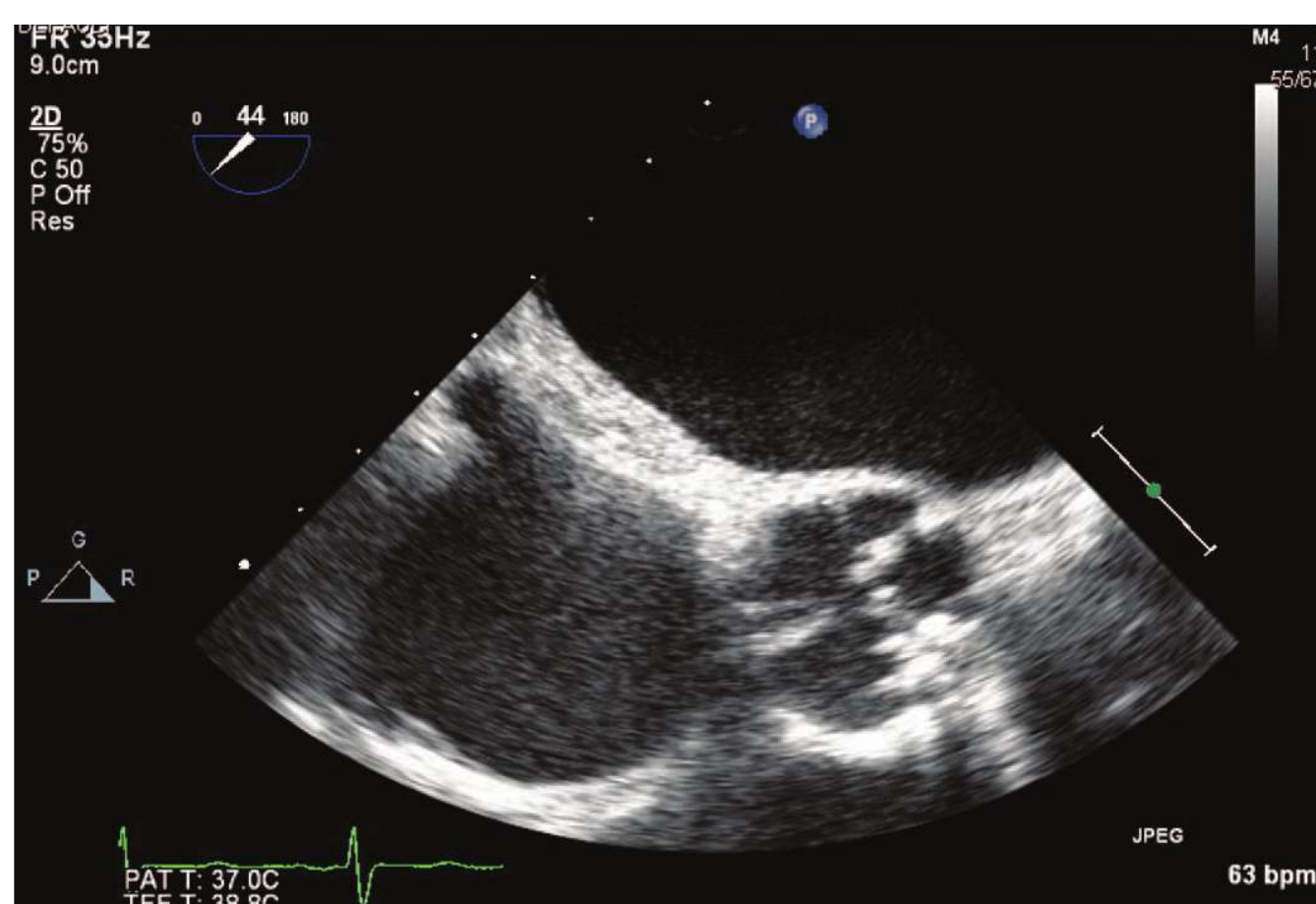


FIGURE 53-10

Transesophageal echocardiogram shows a calcified trileaflet aortic valve (left) with reduced leaflet excursion and a narrowed orifice in peak systole (right).

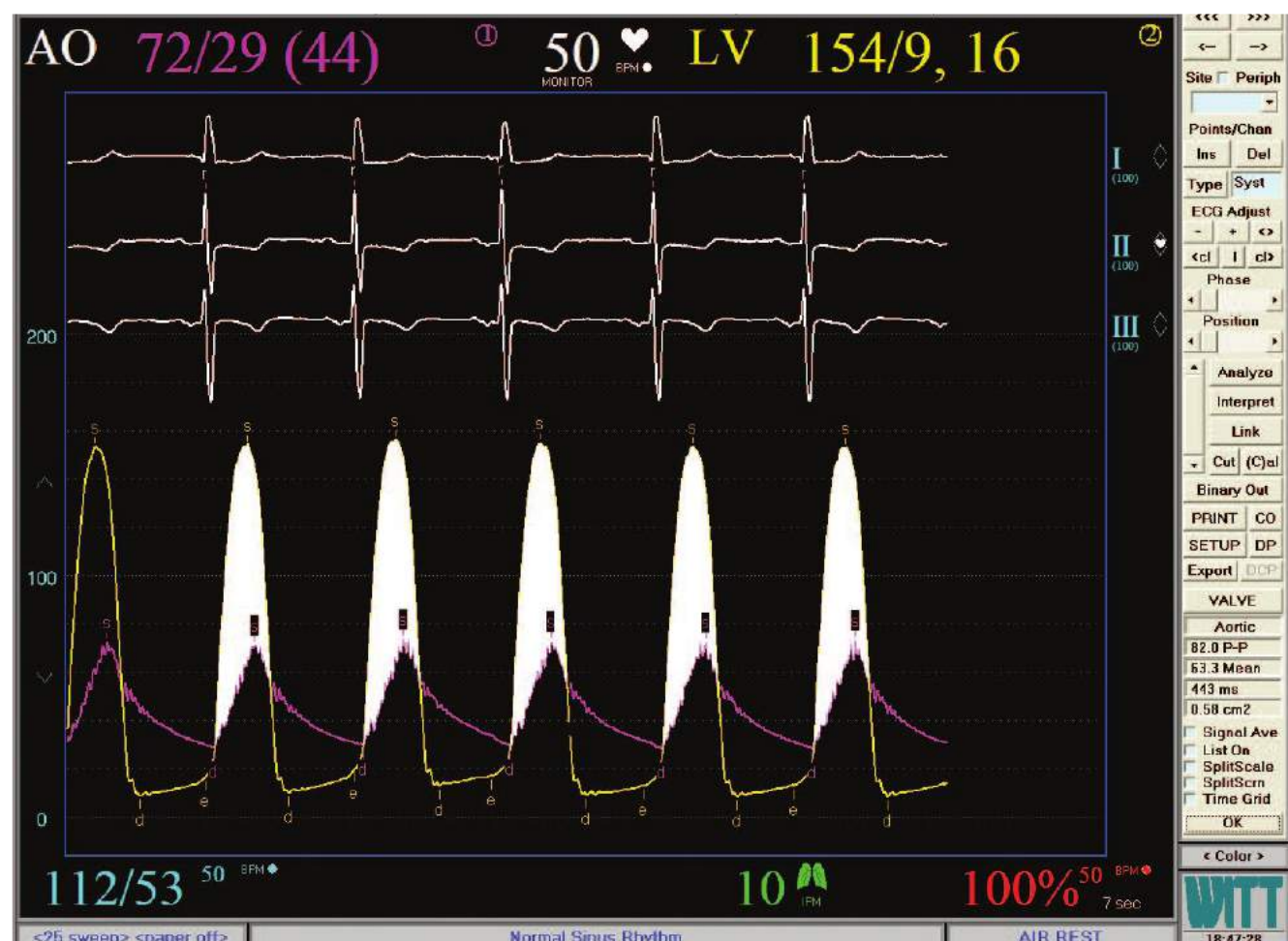


FIGURE 53-11

Hemodynamically significant aortic (AO) stenosis. Simultaneous recording of AO and left ventricle (LV) pressures shows an 82 mmHg peak-to-peak gradient and a 63.3 mmHg mean gradient between the LV (154/9 mmHg) and AO (72/29 mmHg) pressures. This is consistent with an aortic valve area of 0.58 cm².

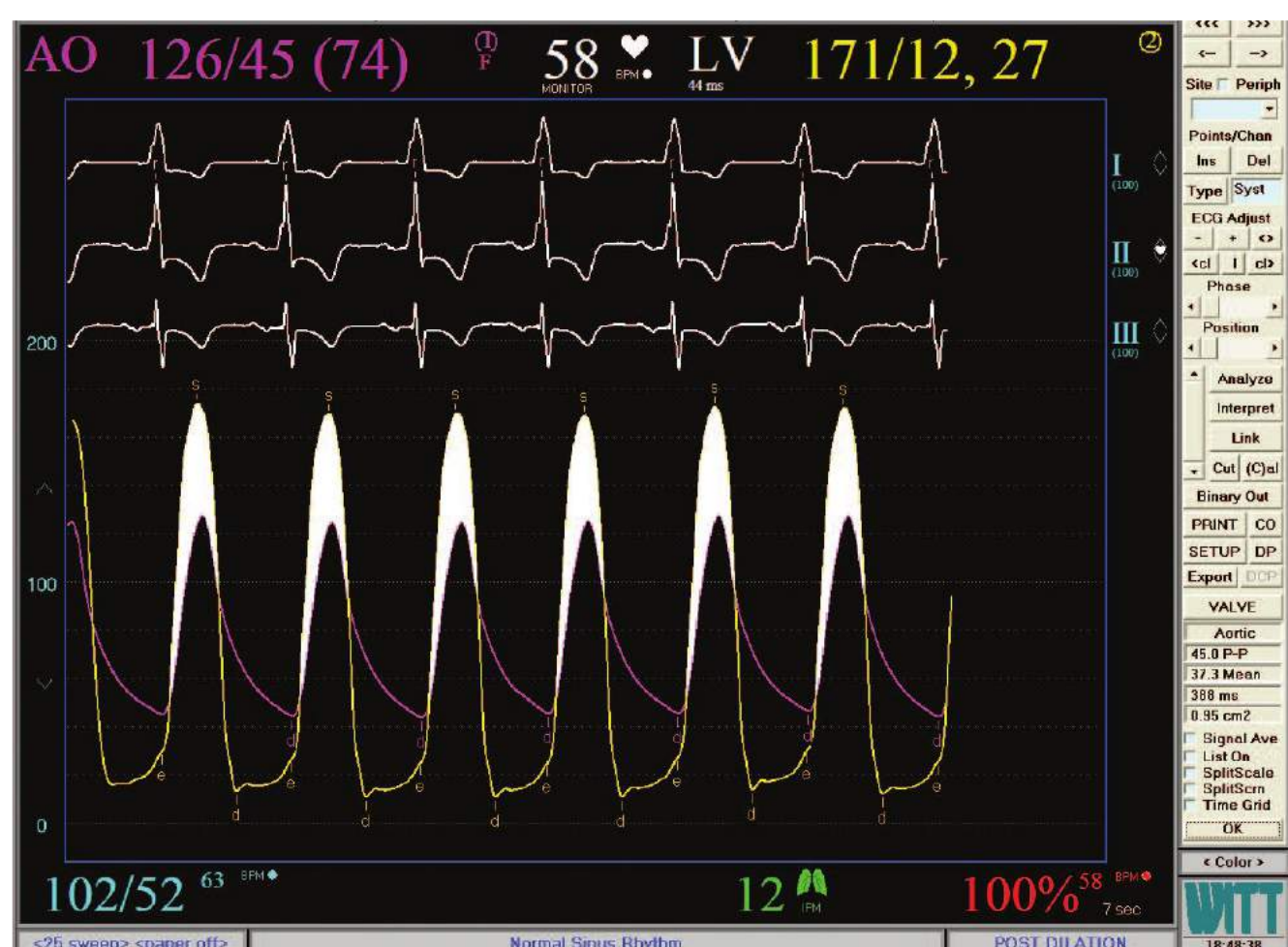


FIGURE 53-12

After balloon valvuloplasty, the LV-AO mean pressure gradient decreased to 37.3 mmHg, indicating that the aortic valve area increased to 0.95 cm².

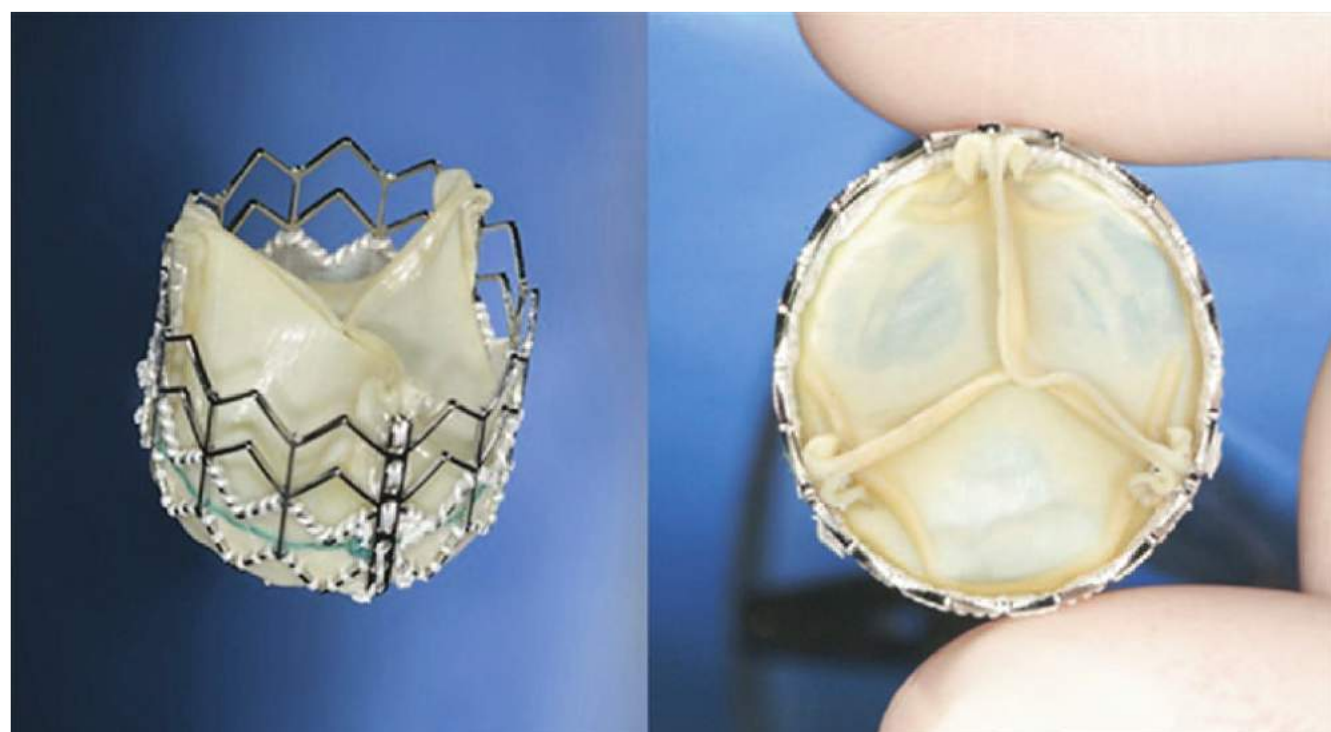


FIGURE 53-13

The Edwards SAPIEN transcatheter heart valve. (Reprinted with permission from AZajarias, AGCribier: J Am Coll Cardiol 53:1829, 2009.)

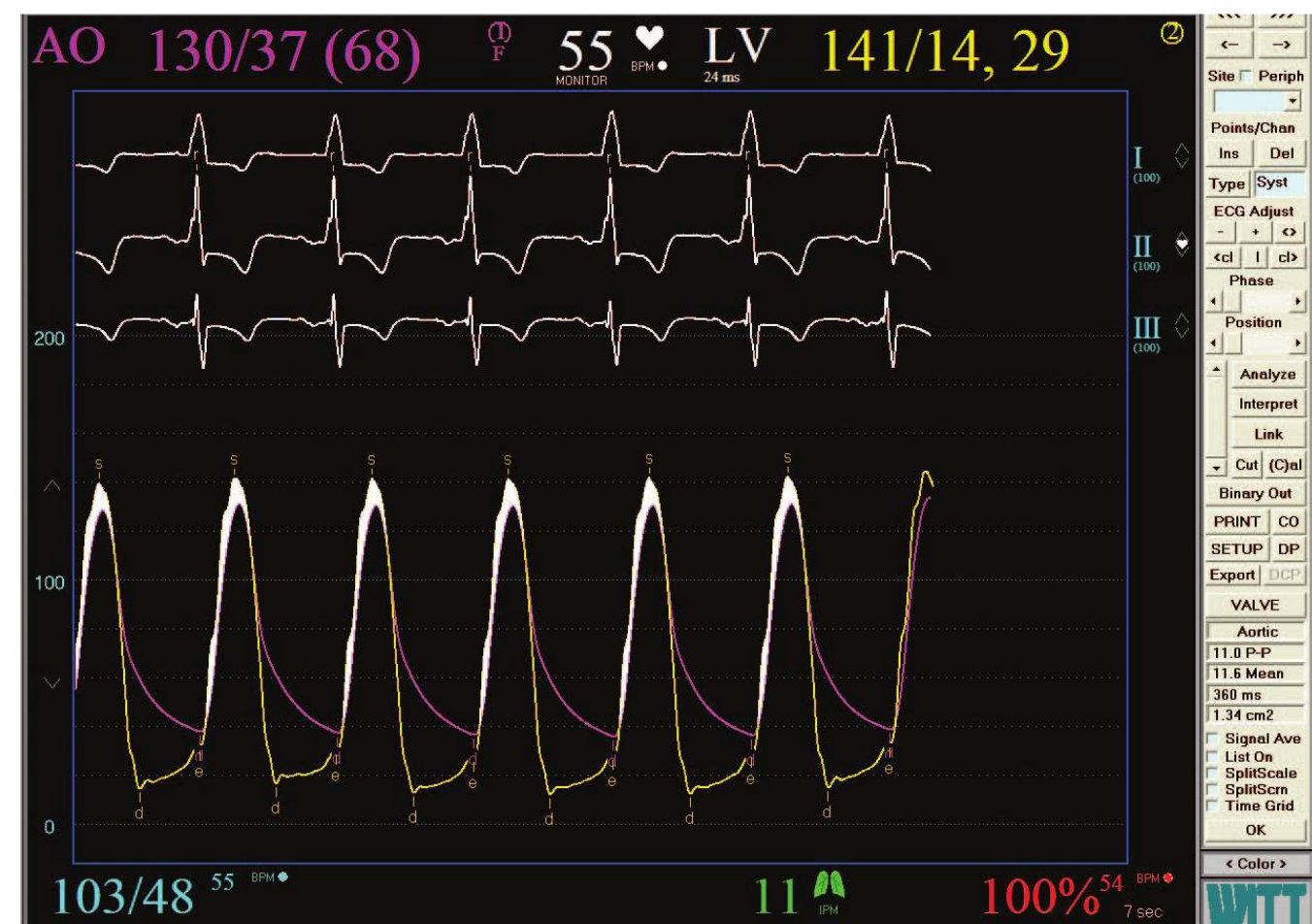


FIGURE 53-14

Once the valve was deployed, the pressure gradient between the LV and AO decreased to 11.6 mmHg, and the functional valve area is 1.34 cm².

- She was referred for transcatheter aortic valve replacement (TAVR) as part of a clinical trial.

SUMMARY

- The prevalence of calcific aortic stenosis is 2–3% in individuals age ≥ 75 years.
- Symptomatic aortic stenosis is associated with an average survival of 2–3 years and an increased risk of sudden death; aortic valve replacement improves both symptoms and survival.
- In high-risk patients with severe aortic stenosis who are not surgical candidates, 1- and 5-year survival rates are ~62% and 38%, respectively.
- TAVR is approved in Europe and was recently approved in the United States as an alternative to surgical aortic valve replacement in high-risk patients.

(Case contributed with permission by Dr. Andrew C. Eisenhauer.)

CASE 9: ATRIAL SEPTAL DEFECT CLOSURE

(Figs. 53-15 to 53-21; Videos 53-51 to 53-53)

- A 48-year-old female with increased shortness of breath, exercise intolerance, and an 18-mm secundum ASD.
- Echocardiogram showed a dilated right atrium (RA) and right ventricle (RV) with evidence of right ventricular volume overload.
- A shunt ratio (Qp/Qs) of 2.3:1 was determined at cardiac catheterization.

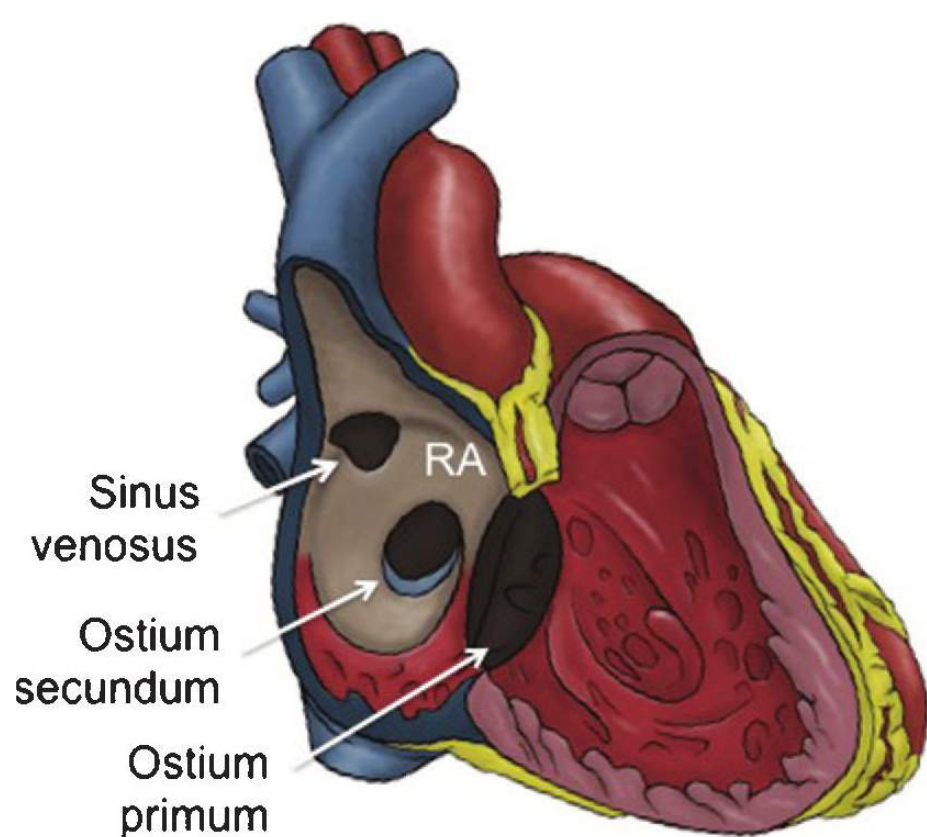


FIGURE 53-15

Anatomic location of common atrial septal defects (ASDs). The most common ASDs are the sinus venosus, ostium secundum, and ostium primum ASDs. The sinus venosus ASD is located at the junction of the superior vena cava (SVC) and the right atrium (RA). This ASD is often associated with anomalous drainage of the right-side pulmonary veins into the RA instead of the left atrium. The secundum ASD is located at the foramen ovale and allows blood to flow between the RA and the left atrium. The primum ASD, also known as an atrioventricular septal defect, connects the RA and right ventricle with the left atrium and ventricle. (Illustration by Justin E. Tribuna.)

- Based on her symptoms, evidence of right-side chamber dilation, and a moderately sized ASD, the patient was referred for percutaneous closure of the ASD.

SUMMARY

- Unrepaired ASDs lead to signs and symptoms of increased pulmonary blood flow and right heart failure, dyspnea, exercise intolerance, fatigue, palpitations and atrial arrhythmias, and pulmonary infections.

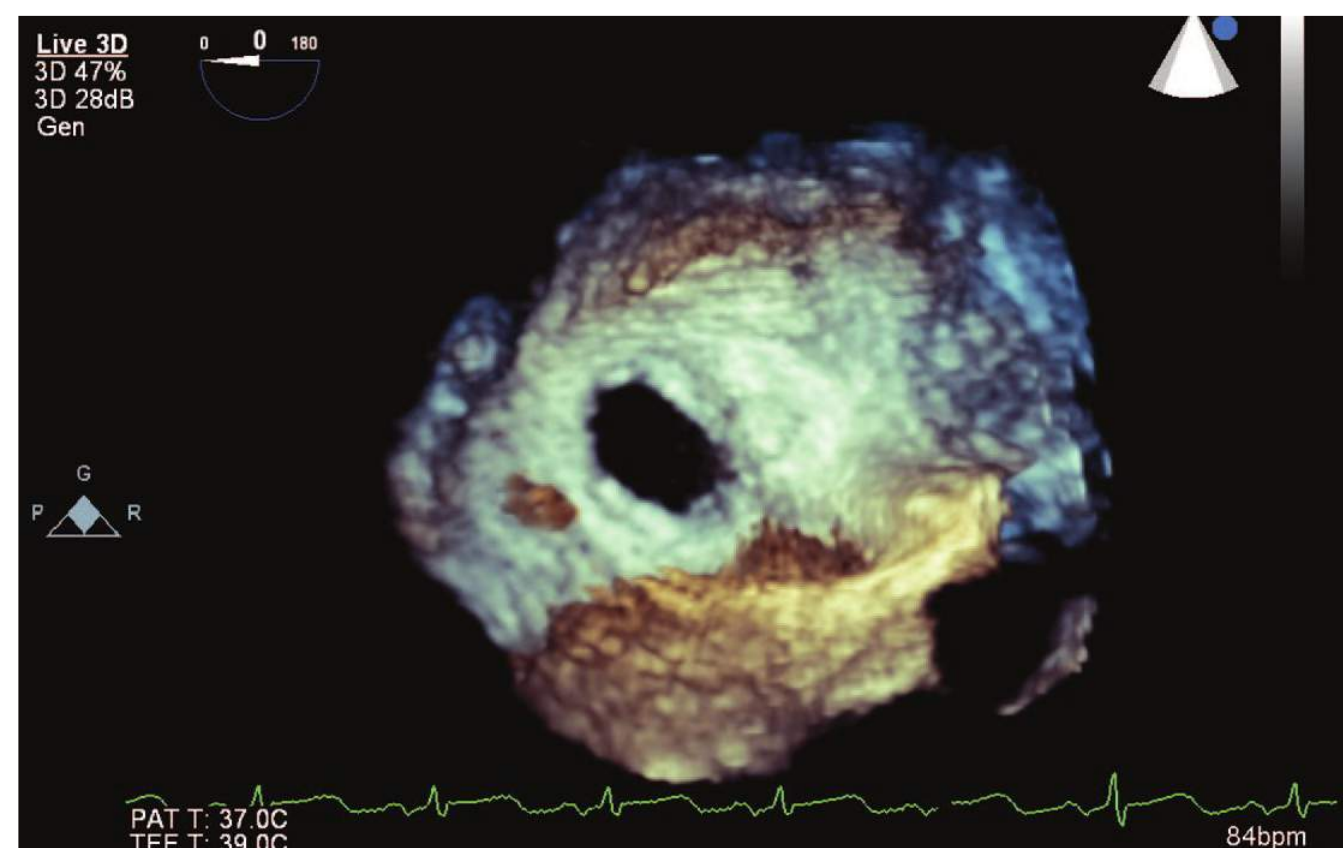


FIGURE 53-17

Three-dimensional echocardiographic reconstruction of the secundum ASD. The ASD is round and has an acceptable margin of tissue to seat a septal occluder device.

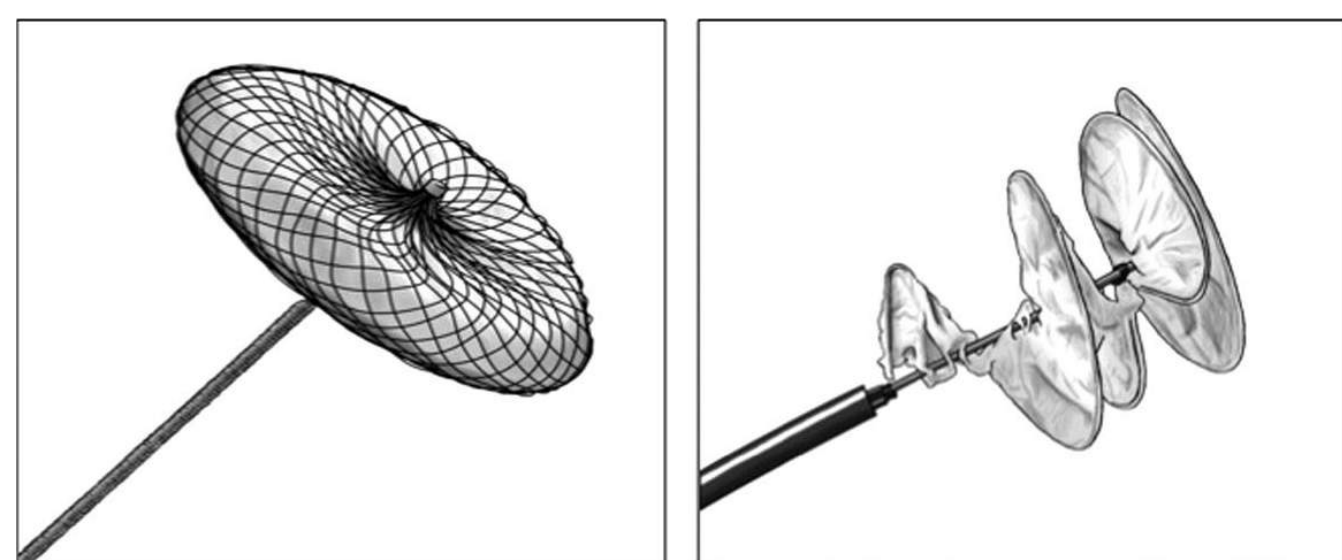


FIGURE 53-18

ASD percutaneous closure devices. The Amplatzer® septal occluder (left) and the HELEX® septal occluder (right) are among the devices used for percutaneous closure of ASDs. The Amplatzer® septal occluder is a plug between two disks that are positioned on each side of the ASD to obstruct blood flow. The HELEX® Septal Occluder is positioned on each side of the ASD to allow circular rings covered with rapidly stretching polytetrafluoroethylene device to limit blood flow. The delivery catheters are detached and the devices are left in place. (Illustration by Justin E. Tribuna.)

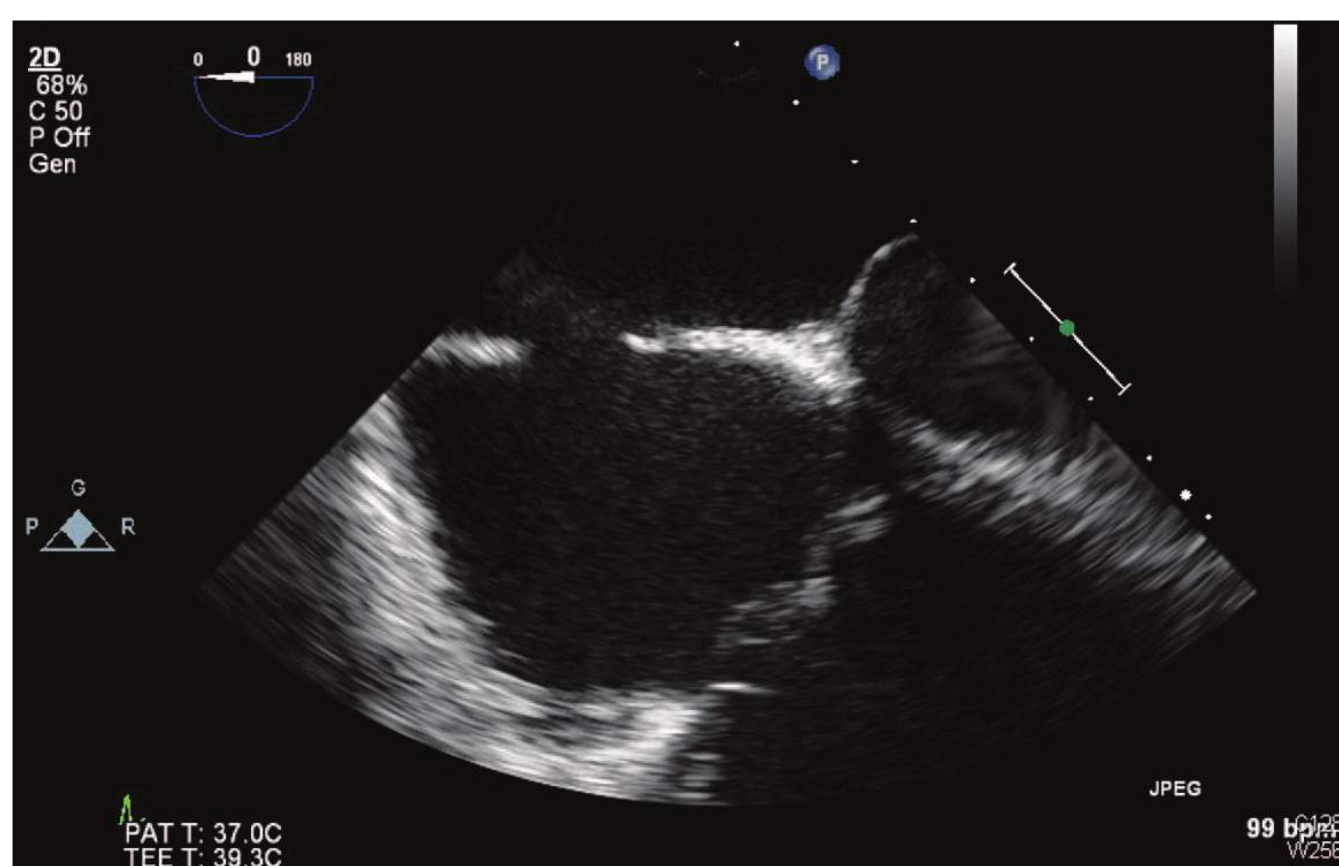
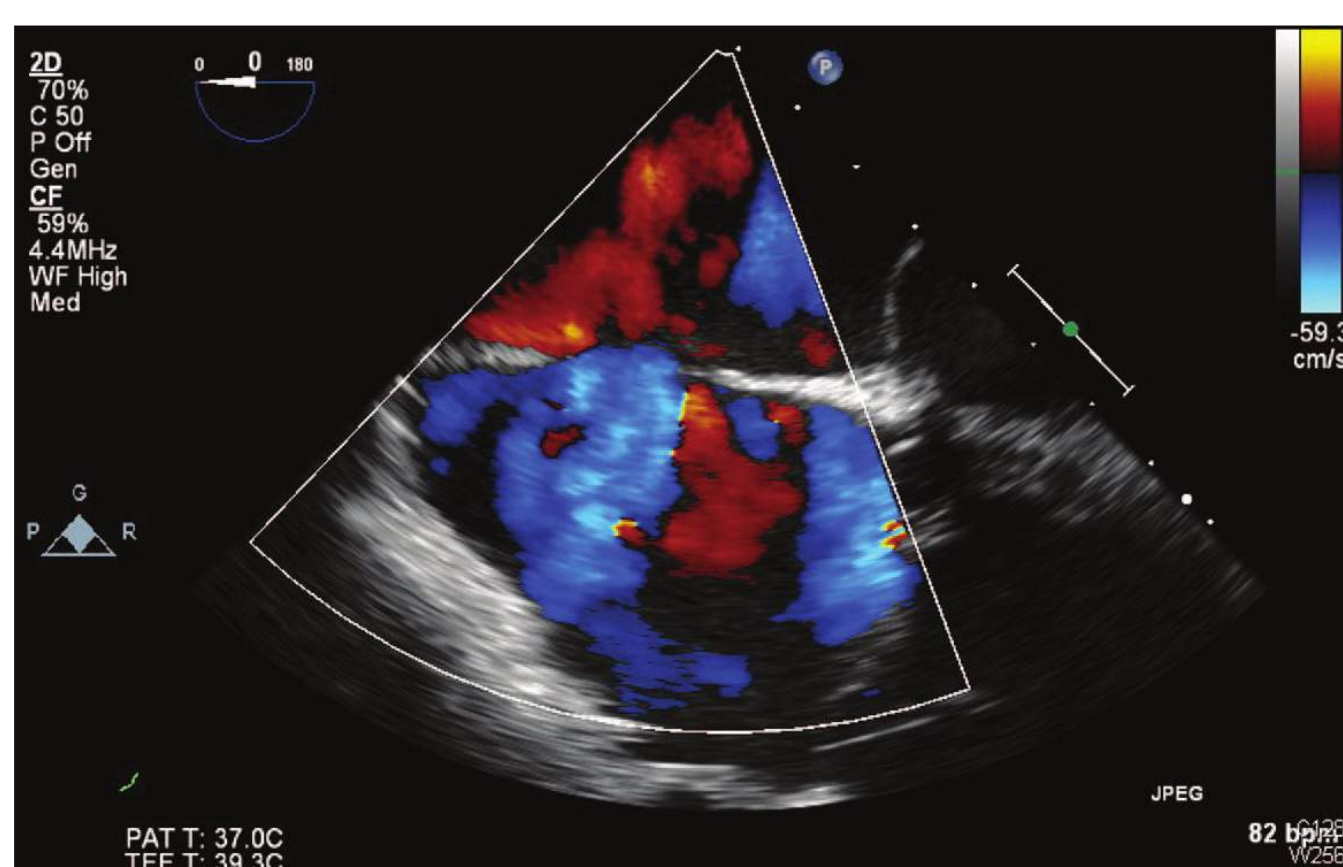


FIGURE 53-16

Transesophageal echocardiogram of a secundum ASD. The ASD is seen as "dropout" in the interatrial septum between the left atrium (LA) and RA (left). Doppler color flow imaging shows blue in the RA consistent with left-to-right flow (right).



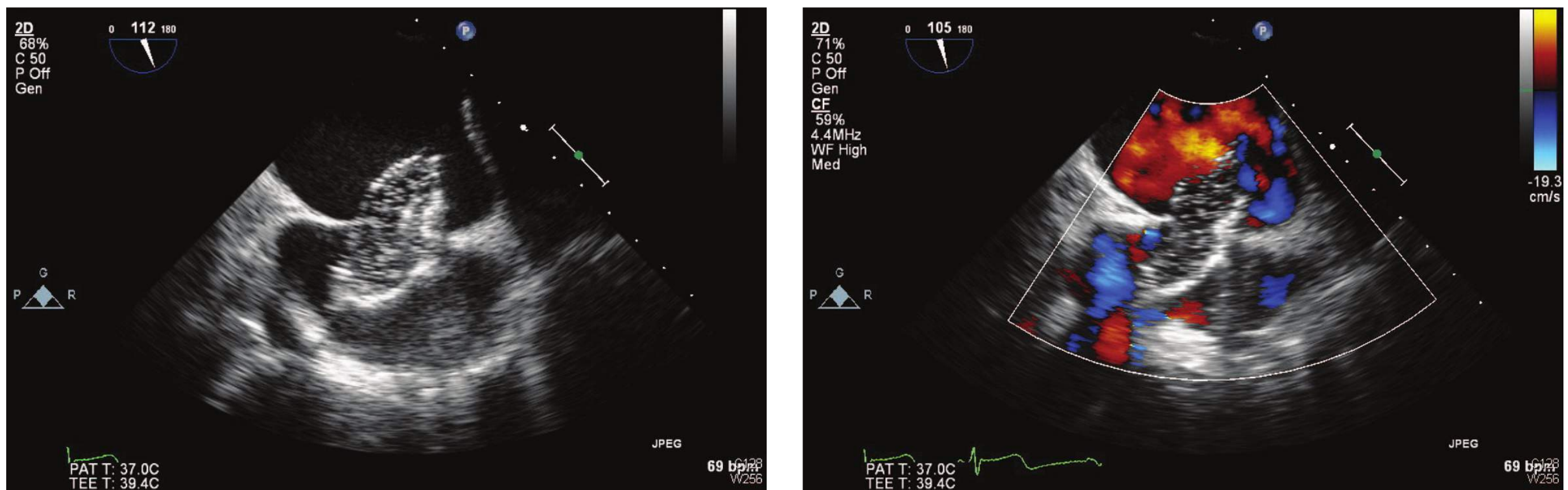


FIGURE 53-19

Transesophageal echocardiogram showing sizing balloon (left) and no flow (right) across the atrial septal defect.

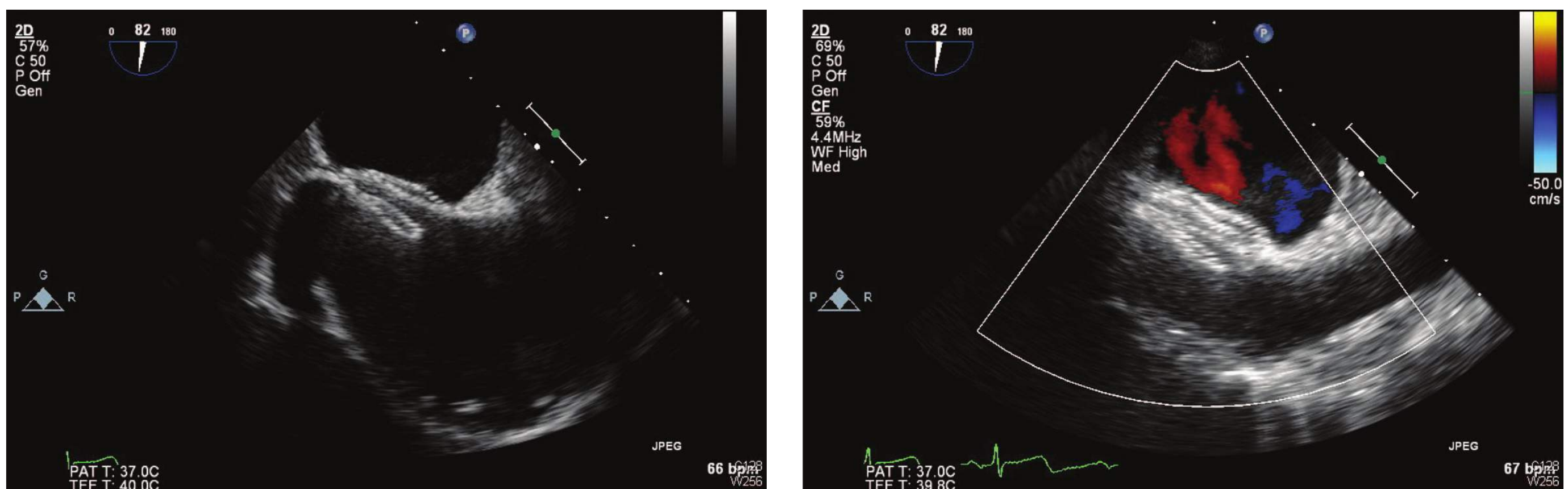


FIGURE 53-20

Amplatzer® septal occluder in place (left). There is no blood flow across the device (right).

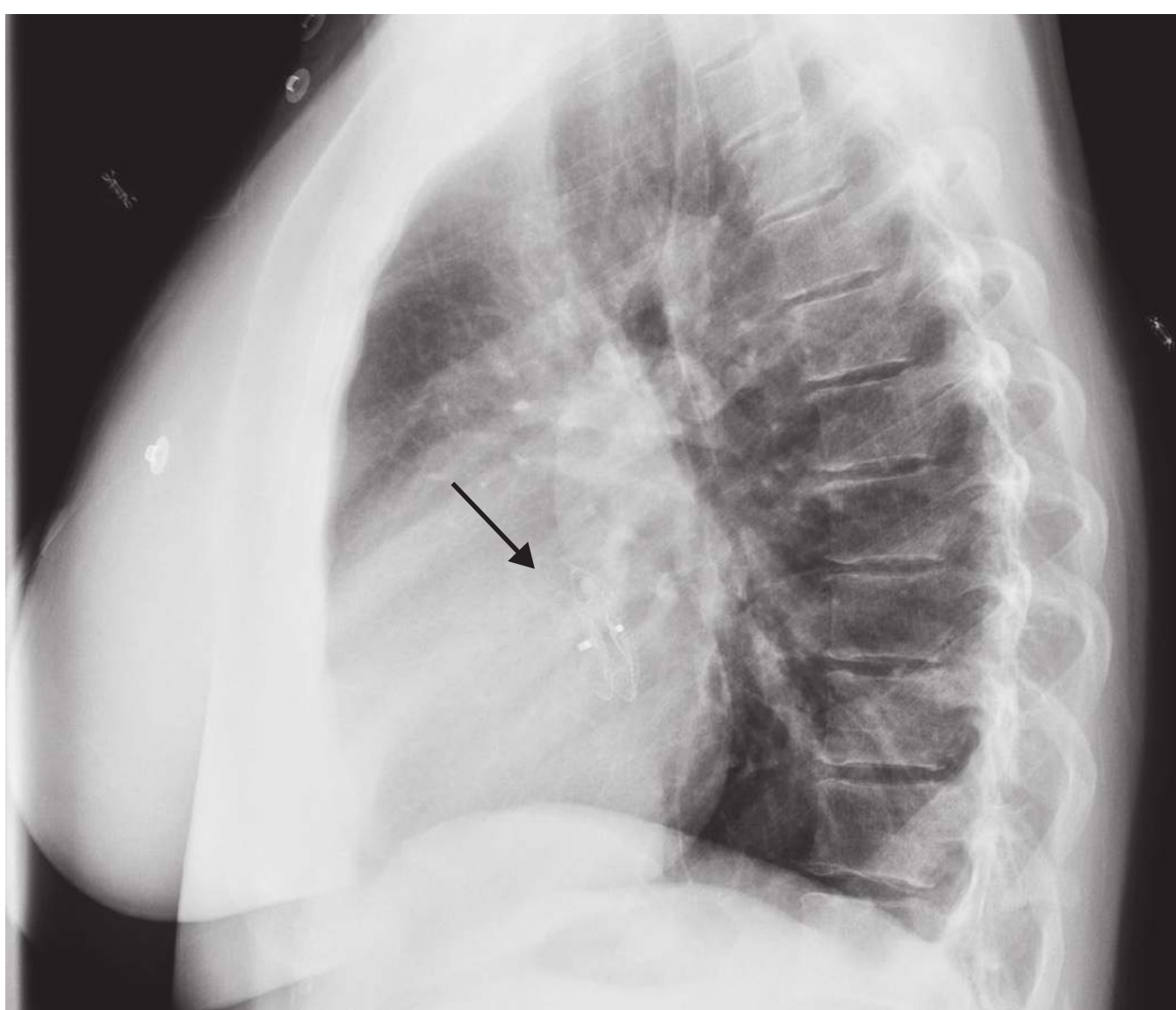


FIGURE 53-21

Postprocedure lateral chest x-ray showing the Amplatzer® septal occluder in place.

- Percutaneous closure of an ASD may be recommended for individuals with a secundum ASD and evidence of RA and RV enlargement with or without symptoms.
- Percutaneous closure is contraindicated in patients with irreversible pulmonary arterial hypertension and no left-to-right shunt. It is not recommended for closure of sinus venosus, coronary sinus, or primum ASDs.
- After the atrial septal occluder device is placed, patients are treated with antiplatelet agents and use antibiotic prophylaxis for certain procedures for 6 months. Follow-up echocardiograms to assess for device migration or erosion, residual shunting, thrombus, or pericardial effusion are recommended at 1 day, 1 month, 6 months, 1 year, and periodically thereafter.

(Case contributed with permission by Dr. Andrew C. Eisenhauer.)

Videos can be accessed via the following link:

<https://www.mhprofessional.com/mediacenter/>

Video 53–1. Baseline left coronary angiogram shows an occluded LCx with left-to-left collaterals originating from LAD septal vessels.

Video 53–2. Attempts to cross the total occlusion in the LCx using a hydrophilic wire and an antegrade approach were not successful with the wire tracking to the right of the trajectory.

Video 53–3. The LAD septal collateral is accessed with a guidewire that is directed toward the distal LCx to cross the total occlusion retrograde.

Video 53–4. The total occlusion is crossed retrograde. The wire is snared in the guide, exteriorized, and used to provide antegrade access to the LCx.

Video 53–5. Antegrade flow in the LCx is restored after balloon inflation.

Video 53–6. Following stenting of the total occlusion, blood flow in the distal vessel is improved and a second significant stenosis is seen.

Video 53–7. Final result after LCx stenting.

Video 53–8. Baseline angiogram of the left coronary circulation shows the significant stenosis in the mid-lad and the bifurcation lesion involving a large diagonal branch.

Video 53–9. Both vessels are accessed with guidewires and pretreated with balloon angioplasty.

Video 53–10. Result after balloon angioplasty.

Video 53–11. Stent being positioned in the LAD.

Video 53–12. LAD poststent result.

Video 53–13. Stent deployed in the diagonal branch through the stent struts in the LAD using the “culotte” technique.

Video 53–14. Diagonal branch poststent result.

Video 53–15. Simultaneous inflation of two 2.5-mm “kissing” balloons.

Video 53–16. Final postbifurcation stenting result.

Video 53–17. The right coronary artery (RCA) is totally occluded with filling defects in the vessel after contrast injection, indicating thrombus is present in the vessel.

Video 53–18. An angioplasty wire is threaded through the thrombotic lesion, but this does not restore blood flow to the distal vessel.

Video 53–19. Result after manual thrombectomy and thrombus extraction. the “culprit” ruptured plaque and residual thrombus are now apparent in the vessel.

Video 53–20. After balloon angioplasty and stenting, thrombus is still present.

Video 53–21. After repeat manual thrombectomy and expansion of the stent, the thrombus is no longer present.

Video 53–22. Final result.

Video 53–23. Saphenous vein graft to a first obtuse marginal branch with an 80% eccentric stenosis in the midgraft.

Video 53–24. A distal protection device is deployed past the lesion.

Video 53–25. Angioplasty balloon inflation with the distal protection device in place.

Video 53–26. Final result **a**fter stent placement.

Video 53–27. Baseline **l**eft coronary artery injection in right anterior oblique (RAO) cranial projection shows a high-grade **calci**fied stenosis in the **l**eft main coronary artery and a **signi**fificant stenosis in the proximal LAD.

Video 53–28. In the **l**eft anterior oblique (LAO) caudal view, the **l**eft main coronary artery lesion can be seen to extend into the ostia **o**f both the LCx and the LAD.

Video 53–29. Guidewires were placed into both the LCx and LAD. **A**fter the **l**eft main coronary artery and LCx are dilated with balloon angioplasty, the proximal LAD is dilated, and a long drug-eluting stent is placed to cover a lesion **d**issection that occurred with wiring **o**f the vessel.

Video 53–30. The **b**ifurcation lesion in the **l**eft main coronary artery extending into the LCx and LAD ostia is treated using a “culotte” technique. First, a drug-eluting stent is placed in the **l**eft main coronary artery and into the proximal LCx.

Video 53–31. Next, the LAD wire is removed and passed through the stent into the distal LAD. A second drug-eluting stent is deployed through the struts **o**f the **l**eft main coronary artery/LCx Stent.

Video 53–32. Following Rewiring **o**f the LCx, both Stents are re-dilated simultaneously (“kissing” balloons).

Video 53–33. The **f**inal result in the LAO caudal view.

Video 53–34. The **f**inal result in the RAO cranial view showing patent **l**eft main, LCx, and LAD coronary arteries.

Video 53–35. Baseline angiogram **o**f the **l**eft coronary circulation in the RAO view shows the total occlusion **o**f the second obtuse

marginal branch with delayed retrograde **f**illing via collateral vessels and a high-grade stenosis in the ramus intermedius.

Video 53–36. A guidewire is passed through the total occlusion, and the lesion is pretreated with balloon angioplasty.

Video 53–37. Following placement **o**f a drug-eluting stent in the lesion, the vessel is widely patent. A third obtuse marginal vessel, not previously seen, now **f**ills **f**aintly (thrombolysis in myocardial **i**nfarction [TIMI] grade 1 **f**low) with contrast but was not treated.

Video 53–38. The ramus intermedius lesion was crossed with a guidewire and pretreated with balloon angioplasty.

Video 53–39. A drug-eluting stent is placed across the ramus lesion and deployed. the **f**inal result shows no residual stenosis in either the ramus or second obtuse marginal vessels.

Video 53–40. Baseline angiogram **o**f the RCA shows a high-grade lesion in the midsegment **o**f the vessel.

Video 53–41. The lesion was pretreated with balloon dilation **f**ollowed by stent deployment.

Video 53–42. The **f**inal result shows no residual stenosis in the mid-RCA.

Video 53–43. Baseline angiogram showing a total occlusion **o**f the proximal LAD within the drug-eluting stent and a **signi**fificant stenosis at the origin **o**f the LCx.

Video 53–44. The LAO view shows the LCx stenosis with a **f**illing **d**efect indicating that thrombus is present in the vessel lumen.

Video 53–45. The LAD lesion was crossed with a guidewire, which resulted in slow **f**illing **o**f the mid-LAD (TIMI 2 Flow) and revealed thrombus **f**illing the stent.

Video 53–46. The **final** result **a**fter LAD and LCx stenting.

The LAD lesion was pretreated with balloon angioplasty, and a bare metal stent was deployed to cover the proximal lesion. The LCx ostial lesion was dilated with balloon angioplasty, and a bare metal stent was placed using a “V stenting” technique.

Video 53–47. Aortogram shows patent coronary arteries and minimal aortic insufficiency.

Video 53–48. Balloon valvuloplasty is **per**formed with rapid ventricular pacing at 180 Beats/Min.

Video 53–49. A 26-mm edwards SAPIEN valve is positioned using **flu**oroscopic and transesophageal echo guidance and deployed.

Video 53–50. Aortogram **a**fter valve deployment shows a **functional** valve with mild aortic insufficiency and without impingement **o**f the coronary ostia.

Video 53–51. A sizing balloon is placed across the ASD.

Video 53–52. An amplatzer[®] septal occluder is being positioned across the ASD.

Video 53–53. The two disks **o**f the device in place across the ASD.

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APPENDIX

LABORATORY VALUES OF CLINICAL IMPORTANCE

Alexander Kratz ■ Michael A. Pesce ■ Robert C. Basner
■ Andrew J. Einstein

This appendix contains tables of reference values for common laboratory tests. A variety of factors can influence reference values. Such variables include the population studied, the duration and means of specimen transport, laboratory methods and instrumentation, and even the type of container used for the collection of the specimen. The reference or “normal” ranges given in this appendix may therefore not be appropriate for all laboratories, and these values should only be used as general guidelines. Whenever possible, reference values provided by the laboratory performing the testing should be used in the interpretation of laboratory data. Values supplied in this appendix reflect typical reference ranges in

nonpregnant adults. Pediatric reference ranges and values in pregnant patients may vary significantly from the data presented in the appendix.

In preparing the appendix, the authors have taken into account the fact that the system of international units (SI, système international d’unités) is used in most countries and in some medical journals. However, clinical laboratories may continue to report values in “traditional” or conventional units. Therefore, both systems are provided in the appendix. The dual system is also used in the text except for those instances in which the numbers remain the same and only the terminology is changed (mmol/L for meq/L or IU/L for mIU/mL), when only the SI units are given.

TABLE 1

HEMATOLOGY AND COAGULATION

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Activated clotting time	WB	70–180 s	70–180 s
Activated protein C resistance (factor V Leiden)	P	Not applicable	Ratio >2.1
ADAMTS13 activity	P	≥0.67	≥67%
ADAMTS13 inhibitor activity	P	Not applicable	≤0.4 U
ADAMTS13 antibody	P	Not applicable	≤18 U
Alpha-2 antiplasmin	P	0.87–1.55	87–155%
Antiphospholipid antibody panel			
PTT-LA (lupus anticoagulant screen)	P	Negative	Negative
Platelet neutralization procedure	P	Negative	Negative
Dilute viper venom screen	P	Negative	Negative
Anticardiolipin antibody	S		
IgG		0–15 arbitrary units	0–15 GPL
IgM		0–15 arbitrary units	0–15 MPL

(continued)

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Beta-2 glycoprotein 1 antibodies	S		
IgG		0–20 arbitrary units	0–20 SGU
IgM		0–20 arbitrary units	0–20 SMU
Antithrombin III	P		
Antigenic		220–390 mg/L	22–39 mg/dL
Functional		0.7–1.30 U/L	70–130%
Anti-Xa assay (heparin assay)	P		
Unfractionated heparin		0.3–0.7 kIU/L	0.3–0.7 IU/mL
Low-molecular-weight heparin		0.5–1.0 kIU/L	0.5–1.0 IU/mL
Danaparoid (Orgaran)		0.5–0.8 kIU/L	0.5–0.8 IU/mL
Autohemolysis test	WB	0.004–0.045	0.4–4.50%
Autohemolysis test with glucose	WB	0.003–0.007	0.3–0.7%
Bleeding time (adult)		<7.1 min	<7.1 min
C4 binding protein	P	305–695 mg/L	30.5–69.5 mg/dL
	S	275–604 mg/L	27.5–60.4 mg/dL
Clot retraction	WB	0.50–1.00/2 h	50–100%/2 h
Cryofibrinogen	P	Negative	Negative
D-dimer	P	220–740 ng/mL FEU	220–740 ng/mL FEU
Differential blood count	WB		
Relative counts			
Neutrophils		0.40–0.70	40–70%
Bands		0.0–0.05	0–5%
Lymphocytes		0.20–0.50	20–50%
Monocytes		0.04–0.08	4–8%
Eosinophils		0.0–0.6	0–6%
Basophils		0.0–0.02	0–2%
Absolute counts			
Neutrophils		$1.42\text{--}6.34 \times 10^9/\text{L}$	$1420\text{--}6340/\text{mm}^3$
Bands		$0\text{--}0.45 \times 10^9/\text{L}$	$0\text{--}450/\text{mm}^3$
Lymphocytes		$0.71\text{--}4.53 \times 10^9/\text{L}$	$710\text{--}4530/\text{mm}^3$
Monocytes		$0.14\text{--}0.72 \times 10^9/\text{L}$	$140\text{--}720/\text{mm}^3$
Eosinophils		$0\text{--}0.54 \times 10^9/\text{L}$	$0\text{--}540/\text{mm}^3$
Basophils		$0\text{--}0.18 \times 10^9/\text{L}$	$0\text{--}180/\text{mm}^3$
Erythrocyte count	WB		
Adult male		$4.30\text{--}5.60 \times 10^{12}/\text{L}$	$4.30\text{--}5.60 \times 10^6/\text{mm}^3$
Adult female		$4.00\text{--}5.20 \times 10^{12}/\text{L}$	$4.00\text{--}5.20 \times 10^6/\text{mm}^3$
Erythrocyte life span	WB		
Normal survival		120 days	120 days
Chromium labeled, half-life ($t_{1/2}$)		25–35 days	25–35 days
Erythrocyte sedimentation rate	WB		
Female		0–20 mm/h	0–20 mm/h
Male		0–15 mm/h	0–15 mm/h

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Euglobulin lysis time	P	7200–14,400 s	120–240 min
Factor II, prothrombin	P	0.50–1.50	50–150%
Factor V	P	0.50–1.50	50–150%
Factor VII	P	0.50–1.50	50–150%
Factor VIII	P	0.50–1.50	50–150%
Factor IX	P	0.50–1.50	50–150%
Factor X	P	0.50–1.50	50–150%
Factor XI	P	0.50–1.50	50–150%
Factor XII	P	0.50–1.50	50–150%
Factor XIII screen	P	Not applicable	Present
Factor inhibitor assay	P	<0.5 Bethesda units	<0.5 Bethesda units
Fibrin(ogen) degradation products	P	0–1 mg/L	0–1 µg/mL
Fibrinogen	P	2.33–4.96 g/L	233–496 mg/dL
Glucose-6-phosphate dehydrogenase (erythrocyte)	WB	<2400 s	<40 min
Ham’s test (acid serum)	WB	Negative	Negative
Hematocrit	WB		
Adult male		0.388–0.464	38.8–46.4
Adult female		0.354–0.444	35.4–44.4
Hemoglobin			
Plasma	P	6–50 mg/L	0.6–5.0 mg/dL
Whole blood	WB		
Adult male		133–162 g/L	13.3–16.2 g/dL
Adult female		120–158 g/L	12.0–15.8 g/dL
Hemoglobin electrophoresis	WB		
Hemoglobin A		0.95–0.98	95–98%
Hemoglobin A ₂		0.015–0.031	1.5–3.1%
Hemoglobin F		0–0.02	0–2.0%
Hemoglobins other than A, A ₂ , or F		Absent	Absent
Heparin-induced thrombocytopenia antibody	P	Negative	Negative
Immature platelet fraction (IPF)	WB	0.011–0.061	1.1–6.1%
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Leukocytes			
Alkaline phosphatase (LAP)	WB	0.2–1.6 µkat/L	13–100 µ/L
Count (WBC)	WB	3.54–9.06 × 10 ⁹ /L	3.54–9.06 × 10 ³ /mm ³
Mean corpuscular hemoglobin (MCH)	WB	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	WB	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	WB	79–93.3 fL	79–93.3 µm ³
Mean platelet volume (MPV)	WB	9.00–12.95 fL	9.00–12.95

(continued)

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Osmotic fragility of erythrocytes	WB		
Direct		0.0035–0.0045	0.35–0.45%
Indirect		0.0030–0.0065	0.30–0.65%
Partial thromboplastin time, activated	P	26.3–39.4 s	26.3–39.4 s
Plasminogen	P		
Antigen		84–140 mg/L	8.4–14.0 mg/dL
Functional		0.70–1.30	70–130%
Plasminogen activator inhibitor 1	P	4–43 µg/L	4–43 ng/mL
Platelet aggregation	PRP	Not applicable	>65% aggregation in response to adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid
Platelet count	WB	165–415 × 10 ⁹ /L	165–415 × 10 ³ /mm ³
Platelet, mean volume	WB	6.4–11 fL	6.4–11.0 µm ³
Prekallikrein assay	P	0.50–1.5	50–150%
Prekallikrein screen	P		No deficiency detected
Protein C	P		
Total antigen		0.70–1.40	70–140%
Functional		0.70–1.30	70–130%
Protein S	P		
Total antigen		0.70–1.40	70–140%
Functional		0.65–1.40	65–140%
Free antigen		0.70–1.40	70–140%
Prothrombin gene mutation G20210A	WB	Not applicable	Not present
Prothrombin time	P	12.7–15.4 s	12.7–15.4 s
Protoporphyrin, free erythrocyte	WB	0.28–0.64 µmol/L of red blood cells	16–36 µg/dL of red blood cells
Red cell distribution width	WB	<0.145	<14.5%
Reptilase time	P	16–23.6 s	16–23.6 s
Reticulocyte count	WB		
Adult male		0.008–0.023 red cells	0.8–2.3% red cells
Adult female		0.008–0.020 red cells	0.8–2.0% red cells
Reticulocyte hemoglobin content	WB	>26 pg/cell	>26 pg/cell
Ristocetin cofactor (functional von Willebrand factor)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
Serotonin release assay	S	<0.2 release	<20% release
Sickle cell test	WB	Negative	Negative
Sucrose hemolysis	WB	<0.1	<10% hemolysis
Thrombin time	P	15.3–18.5 s	15.3–18.5 s
Thrombin-antithrombin (TAT) complex	P	<4 µg/L	<4 ng/mL

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Total eosinophils	WB	150–300 × 10 ⁶ /L	150–300/mm ³
Transferrin receptor	S, P	9.6–29.6 nmol/L	9.6–29.6 nmol/L
Viscosity			
Plasma	P	1.7–2.1	1.7–2.1
Serum	S	1.4–1.8	1.4–1.8
von Willebrand factor (VWF) antigen (factor VIII:R antigen)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
von Willebrand factor collagen binding	P	590–2490 U/L	59–249 U/dL
von Willebrand factor multimers	P	Normal distribution	Normal distribution
White blood cells: see “Leukocytes”			

Abbreviations: JF, joint fluid; P, plasma; PRP, platelet-rich plasma; S, serum; WB, whole blood.

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Acetoacetate	P	49–294 μmol/L	0.5–3.0 mg/dL
Adrenocorticotropin (ACTH)	P	1.3–16.7 pmol/L	6.0–76.0 pg/mL
Alanine aminotransferase (ALT, SGPT)	S	0.12–0.70 μkat/L	7–41 U/L
Albumin	S	40–50 g/L	4.0–5.0 mg/dL
Aldolase	S	26–138 nkat/L	1.5–8.1 U/L
Aldosterone (adult)			
Supine, normal sodium diet	S, P	<443 pmol/L	<16 ng/dL
Upright, normal	S, P	111–858 pmol/L	4–31 ng/dL
Alpha fetoprotein (adult)	S	0–8.5 μg/L	0–8.5 ng/mL
Alpha-1-acid glycoprotein	S	0.50–1.2 g/L	50–120 mg/dL
Alpha-1 antitrypsin	S	1.0–2.0 g/L	100–200 mg/dL
Ammonia, as NH ₃	P	11–35 μmol/L	19–60 μg/dL
Amylase (method dependent)	S	0.34–1.6 μkat/L	20–96 U/L
Androstenedione (adult)	S		
Male		0.81–3.1 nmol/L	23–89 ng/dL
Female			
Premenopausal		0.91–7.5 nmol/L	26–214 ng/dL
Postmenopausal		0.46–2.9 nmol/L	13–82 ng/dL
Angiotensin-converting enzyme (ACE)	S	0.15–1.1 μkat/L	9–67 U/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apolipoprotein A-1	S		
Male		0.94–1.78 g/L	94–178 mg/dL
Female		1.01–1.99 g/L	101–199 mg/dL

(continued)

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Apolipoprotein B	S		
Male		0.55–1.40 g/L	55–140 mg/dL
Female		0.55–1.25 g/L	55–125 mg/dL
Arterial blood gases	WB		
(HCO ₃ ⁻)		22–30 mmol/L	22–30 meq/L
P _{co} 2 (sea level, Fio2 0.21)		4.7–6.0 kPa	35–45 mmHg
pH		7.35–7.45	7.35–7.45
Po2 (sea level, Fio2 0.21, age related)		8.9–13.8 kPa	67–104 mmHg
Carboxyhemoglobin and methemoglobin at pH 7.40 and 37°C		≤0.01	≤1%
Aspartate aminotransferase (AST, SGOT)	S	0.20–0.65 μkat/L	12–38 U/L
Autoantibodies	S		
Anticentromere antibody IgG		≤29 AU/mL	≤29 AU/mL
Antidouble-strand (native) DNA		<25 IU/L	<25 IU/L
Antiglomerular basement membrane antibodies			
Qualitative IgG, IgA		Negative	Negative
Quantitative IgG antibody		≤19 AU/mL	≤19 AU/mL
Antihistone antibodies		<1.0 U	<1.0 U
Anti-Jo-1 antibody		≤29 AU/mL	≤29 AU/mL
Antimitochondrial antibody		Not applicable	<20 units
Antieutrophil cytoplasmic autoantibodies		Not applicable	<1:20
Serine proteinase 3 antibodies		≤19 AU/mL	≤19 AU/mL
Myeloperoxidase antibodies		≤19 AU/mL	≤19 AU/mL
Antinuclear antibody		Not applicable	Negative at 1:40
Antiparietal cell antibody		Not applicable	None detected
Anti-RNP antibody		Not applicable	<1.0 U
Anti-Scl 70 antibody		Not applicable	<1.0 U
Anti-Smith antibody		Not applicable	<1.0 U
Antismooth muscle antibody		Not applicable	<1.0 U
Anti-SSA antibody		Not applicable	<1.0 U
Anti-SSB antibody		Not applicable	Negative
Antithyroglobulin antibody		<40 kIU/mL	<40 IU/mL
Antithyroid peroxidase antibody		<35 kIU/L	<35 IU/L
B-type natriuretic peptide (BNP)	P	Age and gender specific: <100 ng/L	Age and gender specific: <100 pg/mL
Bence Jones protein, serum qualitative	S	Not applicable	None detected
Bence Jones protein, serum quantitative	S		
Free kappa		3.3–19.4 mg/L	0.33–1.94 mg/dL
Free lambda		5.7–26.3 mg/L	0.57–2.63 mg/dL
K/L ratio		0.26–1.65	0.26–1.65
Beta-2-microglobulin	S	1.1–2.4 mg/L	1.1–2.4 mg/L

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Bile acids	S		
Cholic acid		0–1.9 µmol/L	0–1.9 µmol/L
Chenodeoxycholic acid		0–3.4 µmol/L	0–3.4 µmol/L
Deoxycholic acid		0–2.5 µmol/L	0–2.5 µmol/L
Ursodeoxycholic acid		0–1.0 µmol/L	0–1.0 µmol/L
Total		0–7.0 µmol/L	0–7.0 µmol/L
Bilirubin	S		
Total		5.1–22 µmol/L	0.3–1.3 mg/dL
Direct		1.7–6.8 µmol/L	0.1–0.4 mg/dL
Indirect		3.4–15.2 µmol/L	0.2–0.9 mg/dL
C-peptide	S	0.27–1.19 nmol/L	0.8–3.5 ng/mL
Cl-esterase-inhibitor protein	S	210–390 mg/L	21–39 mg/dL
CA 125	S	<35 kU/L	<35 U/mL
CA 19-9	S	<37 kU/L	<37 U/mL
CA 15-3	S	<33 kU/L	<33 U/mL
CA 27-29	S	0–40 kU/L	0–40 U/mL
Calcitonin	S		
Male		0–7.5 ng/L	0–7.5 pg/mL
Female		0–5.1 ng/L	0–5.1 pg/mL
Calcium	S	2.2–2.6 mmol/L	8.7–10.2 mg/dL
Calcium, ionized	WB	1.12–1.32 mmol/L	4.5–5.3 mg/dL
Carbon dioxide content (TCO ₂)	P (sea level)	22–30 mmol/L	22–30 meq/L
Carboxyhemoglobin (carbon monoxide content)	WB		
Nonsmokers (in a nonsmoking environment)		0.0–0.025	0–2.5% of total hemoglobin (Hgb) value
Smokers		0.04–0.09	4–9% of total Hgb value
Loss of consciousness and death		>0.50	>50% of total Hgb value
Carcinoembryonic antigen (CEA)	S		
Nonsmokers		0.0–3.0 µg/L	0.0–3.0 ng/mL
Smokers		0.0–5.0 µg/L	0.0–5.0 ng/mL
Ceruloplasmin	S	250–630 mg/L	25–63 mg/dL
Chloride	S	102–109 mmol/L	102–109 meq/L
Cholesterol (LCL, Total, HDL): Ranges depend on individual patient factors; see 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol			
Cholinesterase	S	5–12 kU/L	5–12 U/mL
Chromogranin A	S	0–95 µg/L	0–95 ng/mL
Complement	S		
C3		0.83–1.77 g/L	83–177 mg/dL
C4		0.16–0.47 g/L	16–47 mg/dL
Complement total		60–144 CAE units	60–144 CAE units
Cortisol			
Fasting, 8 am–12 noon	S	138–690 nmol/L	5–25 µg/dL
12 noon–8 pm		138–414 nmol/L	5–15 µg/dL
8 pm–8 am		0–276 nmol/L	0–10 µg/dL
C-reactive protein	S	<10 mg/L	<10 mg/L

(continued)

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
C-reactive protein, high sensitivity	S	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L
Creatine kinase (total)	S		
Females		0.66–4.0 µkat/L	39–238 U/L
Males		0.87–5.0 µkat/L	51–294 U/L
Creatine kinase-MB	S		
Mass		0.0–5.5 µg/L	0.0–5.5 ng/mL
Fraction of total activity (by electrophoresis)		0–0.04	0–4.0%
Creatinine	S		
Female		44–80 µmol/L	0.5–0.9 mg/dL
Male		53–106 µmol/L	0.6–1.2 mg/dL
Cryoglobulins	S	Not applicable	None detected
Cyclic citrullinated peptide (CCP) antibody (IgG)	S	Negative: <20 units Weak positive: 20–39 units Moderate positive: 40–59 Units Strong positive: ≥60 units	Negative: <20 units Weak positive: 20–39 units Moderate positive: 40–59 units Strong positive: ≥60 Units
Cystatin C	S	0.5–1.0 mg/L	0.5–1.0 mg/L
Deamidated gliadin peptide (DGP) antibody, IgA	S		
Negative		≤19 units	≤19 units
Weak positive		20–30 units	20–30 units
Positive		≥31 units	≥31 units
Deamidated gliadin peptide (DGP) antibody, IgG	S		
Negative		≤19 units	≤19 units
Weak positive		20–30 units	20–30 units
Positive		≥31 units	≥31 units
Dehydroepiandrosterone (DHEA) (adult)			
Male	S	6.2–43.4 nmol/L	180–1250 ng/dL
Female		4.5–34.0 nmol/L	130–980 ng/dL
Dehydroepiandrosterone (DHEA) sulfate	S		
Male (adult)		100–6190 µg/L	10–619 µg/dL
Female (adult, premenopausal)		120–5350 µg/L	12–535 µg/dL
Female (adult, postmenopausal)		300–2600 µg/L	30–260 µg/dL
11-Deoxycortisol (adult) (compound S)	S	0.34–4.56 nmol/L	12–158 ng/dL
Dihydrotestosterone			
Male	S, P	1.03–2.92 nmol/L	30–85 ng/dL
Female		0.14–0.76 nmol/L	4–22 ng/dL
Dopamine	P	0–130 pmol/L	0–20 pg/mL
Endomysial antibody, IgA	S	<1:10	<1:10
Endomysial antibody, IgG	S	<1:10	<1:10

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Epinephrine	P		
Supine (30 min)		<273 pmol/L	<50 pg/mL
Sitting		<328 pmol/L	<60 pg/mL
Standing (30 min)		<491 pmol/L	<90 pg/mL
Erythropoietin	S	4–27 U/L	4–27 U/L
Estradiol	S, P		
Female			
Menstruating:			
Follicular phase		74–532 pmol/L	<20–145 pg/mL
Midcycle peak		411–1626 pmol/L	112–443 pg/mL
Luteal phase		74–885 pmol/L	<20–241 pg/mL
Postmenopausal		217 pmol/L	<59 pg/mL
Male		74 pmol/L	<20 pg/mL
Estrone	S, P		
Female			
Menstruating:			
Follicular phase		<555 pmol/L	<150 pg/mL
Luteal phase		<740 pmol/L	<200 pg/mL
Postmenopausal		11–118 pmol/L	3–32 pg/mL
Male		33–133 pmol/L	9–36 pg/mL
Fatty acids, free (nonesterified)	P	0.1–0.6 mmol/L	2.8–16.8 mg/dL
Ferritin	S		
Female		10–150 µg/L	10–150 ng/mL
Male		29–248 µg/L	29–248 ng/mL
Follicle-stimulating hormone (FSH)	S, P		
Female			
Menstruating			
Follicular phase		3.0–20.0 IU/L	3.0–20.0 mIU/mL
Ovulatory phase		9.0–26.0 IU/L	9.0–26.0 mIU/mL
Luteal phase		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Postmenopausal		18.0–153.0 IU/L	18.0–153.0 mIU/mL
Male		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Fructosamine	S	<285 µmol/L	<285 µmol/L
Galectin-3	S		
Low risk		≤17.8 µg/L	≤17.8 ng/mL
Intermediate risk		17.9–25.9 µg/L	17.9–25.9 ng/mL
Higher risk		>25.9 µg/L	>25.9 ng/mL
Gamma glutamyltransferase	S	0.15–0.99 µkat/L	9–58 U/L
Gastrin	S	<100 ng/L	<100 pg/mL
Glucagon	P	40–130 ng/L	40–130 pg/mL
Glucose	WB	3.6–5.3 mmol/L	65–95 mg/dL
Glucose (fasting)	P		
Normal		4.2–5.6 mmol/L	75–100 mg/dL
Increased risk for diabetes		5.6–6.9 mmol/L	100–125 mg/dL

(continued)

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Diabetes mellitus		Fasting ≥ 7.0 mmol/L A 2-h level of ≥ 11.1 mmol/L during an oral glucose tolerance test A random glucose level of ≥ 11.1 mmol/L in patients with symptoms of hyperglycemia	Fasting ≥ 126 mg/dL A 2-h level of ≥ 200 mg/dL during an oral glucose tolerance test A random glucose level of ≥ 200 mg/dL in patients with symptoms of hyperglycemia
Growth hormone	S	0–5 $\mu\text{g/L}$	0–5 ng/mL
Hemoglobin A _{1c}	WB	0.04–0.06 Hgb fraction	4.0–5.6%
Prediabetes		0.057–0.064 Hgb fraction	5.7–6.4%
Diabetes mellitus		A hemoglobin A _{1c} level of ≥ 0.065 Hgb fraction as suggested by the American Diabetes Association	A hemoglobin A _{1c} level of $\geq 6.5\%$ as suggested by the American Diabetes Association
Hemoglobin A _{1c} with estimated average glucose (eAG)	WB	$\text{eAg (mmol/L)} = 1.59 \times \text{HbA}_{1c} - 2.59$	$\text{eAg (mg/dL)} = 28.7 \times \text{HbA}_{1c} - 46.7$
Homocysteine	P	4.4–10.8 $\mu\text{mol/L}$	4.4–10.8 $\mu\text{mol/L}$
Human chorionic gonadotropin (HCG)	S		
Nonpregnant female		< 5 IU/L	< 5 mIU/mL
1–2 weeks postconception		9–130 IU/L	9–130 mIU/mL
2–3 weeks postconception		75–2600 IU/L	75–2600 mIU/mL
3–4 weeks postconception		850–20,800 IU/L	850–20,800 mIU/mL
4–5 weeks postconception		4000–100,200 IU/L	4000–100,200 mIU/mL
5–10 weeks postconception		11,500–289,000 IU/L	11,500–289,000 mIU/mL
10–14 weeks postconception		18,300–137,000 IU/L	18,300–137,000 mIU/mL
Second trimester		1400–53,000 IU/L	1400–53,000 mIU/mL
Third trimester		940–60,000 IU/L	940–60,000 mIU/mL
Human epididymis protein 4 (HE-4)	S	0–150 pmol/L	0–150 pmol/L
β -Hydroxybutyrate	P	60–170 $\mu\text{mol/L}$	0.6–1.8 mg/dL
17-Hydroxyprogesterone (adult)	S		
Male		< 4.17 nmol/L	< 139 ng/dL
Female			
Follicular phase		0.45–2.1 nmol/L	15–70 ng/dL
Luteal phase		1.05–8.7 nmol/L	35–290 ng/dL
Immunofixation	S	Not applicable	No bands detected
Immunoglobulin, quantitation (adult)			
IgA	S	0.70–3.50 g/L	70–350 mg/dL
IgD	S	0–140 mg/L	0–14 mg/dL
IgE	S	1–87 kIU/L	1–87 IU/mL
IgG	S	7.0–17.0 g/L	700–1700 mg/dL
IgG ₁	S	2.7–17.4 g/L	270–1740 mg/dL
IgG ₂	S	0.3–6.3 g/L	30–630 mg/dL
IgG ₃	S	0.13–3.2 g/L	13–320 mg/dL
IgG ₄	S	0.11–6.2 g/L	11–620 mg/dL
IgM	S	0.50–3.0 g/L	50–300 mg/dL

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Inhibin A	S		
Males		≤2.0 ng/L	≤2.0 pg/mL
Females			
Early follicular phase		1.8–17.3 ng/L	1.8–17.3 pg/mL
Mid follicular phase		3.5–31.7 ng/L	3.5–17.3 pg/mL
Late follicular phase		9.8–90.3 ng/L	9.8–90.3 pg/mL
Midcycle		16.9–91.8 ng/L	16.9–91.8 pg/mL
Early luteal phase		16.1–97.5 ng/L	16.1–97.5 pg/mL
Mid luteal phase		3.9–87.7 ng/L	3.9–87.7 pg/mL
Late luteal phase		2.7–47.1 ng/L	2.7–47.1 pg/mL
Postmenopausal		<1.0–2.1 ng/L	<1.0–2.1 pg/mL
Insulin	S, P	14.35–143.5 pmol/L	2–20 μU/mL
Iron	S	7–25 μmol/L	41–141 μg/dL
Iron-binding capacity	S	45–73 μmol/L	251–406 μg/dL
Iron-binding capacity saturation	S	0.16–0.35	16–35%
Ischemia-modified albumin	S	<85 kU/L	<85 U/mL
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Ketone (acetone)	S	Negative	Negative
Lactate	P, arterial	0.5–1.6 mmol/L	4.5–14.4 mg/dL
	P, venous	0.5–2.2 mmol/L	4.5–19.8 mg/dL
Lactate dehydrogenase	S	2.0–3.8 μkat/L	115–221 U/L
Lamellar body count	AMF		
Immature		<15,000/μL	<15,000/μL
Indeterminate		15,000–50,000/μL	15,000–50,000/μL
Mature		>50,000/μL	>50,000/μL
Lecithin/sphingomyelin (L/S) ratio	AMF		
Immature		≤1.5	≤1.5
Transitional		1.5–1.9	1.5–1.9
Mature		≥2.0–2.5	≥2.0–2.5
Lipase	S	0.51–0.73 μkat/L	3–43 U/L
Lipoprotein (a)	S	0–300 mg/L	0–30 mg/dL
Lipoprotein-associated phospholipase A2	S, P	0–234 μg/L	0–234 ng/mL
Luteinizing hormone (LH)	S, P		
Female			
Menstruating			
Follicular phase		2.0–15.0 U/L	2.0–15.0 mIU/mL
Ovulatory phase		22.0–105.0 U/L	22.0–105.0 mIU/mL
Luteal phase		0.6–19.0 U/L	0.6–19.0 mIU/mL
Postmenopausal		16.0–64.0 U/L	16.0–64.0 mIU/mL
Male		2.0–12.0 U/L	2.0–12.0 mIU/mL
Magnesium	S	0.62–0.95 mmol/L	1.5–2.3 mg/dL
Metanephrine	P	<0.5 nmol/L	<100 pg/mL
Methemoglobin	WB	0.0–0.01	0–1% of total Hgb value
Myoglobin	S		
Male		20–71 μg/L	20–71 μg/L
Female		25–58 μg/L	25–58 μg/L

(continued)

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Norepinephrine	P		
Supine (30 min)		650–2423 pmol/L	110–410 pg/mL
Sitting		709–4019 pmol/L	120–680 pg/mL
Standing (30 min)		739–4137 pmol/L	125–700 pg/mL
N-telopeptide (cross-linked), NTx	S		
Female, premenopausal		6.2–19.0 nmol BCE	6.2–19.0 nmol BCE
Male		5.4–24.2 nmol BCE	5.4–24.2 nmol BCE
NT-proBNP	S, P	<125 ng/Lup to 75 years <450 ng/L>75 years	<125 pg/mLup to 75 years <450 pg/mL>75 years
5' Nucleotidase	S	0.00–0.19 µkat/L	0–11 U/L
Osmolality	P	275–295 mOsmol/kg serum water	275–295 mOsmol/kg serum water
Osteocalcin	S	11–50 µg/L	11–50 ng/mL
Oxygen content (age and gender related)	WB		
Arterial (sea level)		17–21 mL/dL	17–21 vol%
Venous (sea level)		10–16 mL/dL	10–16 vol%
Oxygen saturation (sea level)	WB	Fraction:	Percent:
Arterial		0.91–1.0	91–100%
Venous, arm		0.60–0.85	60–85%
Parathyroid hormone (intact)	S	8–51 ng/L	8–51 pg/mL
Phosphatase, alkaline	S	0.56–1.63 µkat/L	33–96 U/L
Phosphatase, alkaline bone	S		
Male		≤20 µg/L	≤20 ng/mL
Female			
Premenopausal		≤14 µg/L	≤14 ng/mL
Postmenopausal		≤22 µg/L	≤22 ng/mL
Phosphorus, inorganic	S	0.81–1.4 mmol/L	2.5–4.3 mg/dL
Potassium	S	3.5–5.0 mmol/L	3.5–5.0 meq/L
Prealbumin (transthyretin)	S	170–340 mg/L	17–34 mg/dL
Procalcitonin	S	<0.1 µg/L	<0.1 ng/mL
Progesterone	S, P		
Female: (follicular)		<3.18 nmol/L	<1.0 ng/mL
Midluteal		9.54–63.6 nmol/L	3–20 ng/mL
Male		<3.18 nmol/L	<1.0 ng/mL
Prolactin	S		
Male		53–360 mg/L	2.5–17 ng/mL
Female		40–530 mg/L	1.9–25 ng/mL
Prostate-specific antigen (PSA)	S	0.0–4.0 µg/L	0.0–4.0 ng/mL
Prostate-specific antigen, free	S	With total PSA between 4 and 10 µg/Land when the free PSA is:	With total PSA between 4 and 10 ng/mLand when the free PSA is:

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
		>0.25 decreased risk of prostate cancer	>25% decreased risk of prostate cancer
		<0.10 increased risk of prostate cancer	<10% increased risk of prostate cancer
Protein fractions:	S		
Albumin		35–55 g/L	3.5–5.5 g/dL (50–60%)
Globulin		20–35 g/L	2.0–3.5 g/dL (40–50%)
Alpha-1		2–4 g/L	0.2–0.4 g/dL (4.2–7.2%)
Alpha-2		5–9 g/L	0.5–0.9 g/dL (6.8–12%)
Beta		6–11 g/L	0.6–1.1 g/dL (9.3–15%)
Gamma		7–17 g/L	0.7–1.7 g/dL (13–23%)
Protein, total	S	67–86 g/L	6.7–8.6 g/dL
Pyruvate	P	40–130 µmol/L	0.35–1.14 mg/dL
Retinol-binding protein	S	0.71–2.9 µmol/L	1.5–6.0 mg/dL
Rheumatoid factor	S	<15 kIU/L	<15 IU/mL
Serotonin	WB	0.28–1.14 µmol/L	50–200 ng/mL
Serum protein electrophoresis	S	Not applicable	Normal pattern
Sex hormone–binding globulin (adult)	S		
Male		11–80 nmol/L	11–80 nmol/L
Female		30–135 nmol/L	30–135 nmol/L
Sodium	S	136–146 mmol/L	136–146 meq/L
Somatomedin-C (IGF-1) (adult)	S		
16 years		226–903 µg/L	226–903 ng/mL
17 years		193–731 µg/L	193–731 ng/mL
18 years		163–584 µg/L	163–584 ng/mL
19 years		141–483 µg/L	141–483 ng/mL
20 years		127–424 µg/L	127–424 ng/mL
21–25 years		116–358 µg/L	116–358 ng/mL
26–30 years		117–329 µg/L	117–329 ng/mL
31–35 years		115–307 µg/L	115–307 ng/mL
36–40 years		119–204 µg/L	119–204 ng/mL
41–45 years		101–267 µg/L	101–267 ng/mL
46–50 years		94–252 µg/L	94–252 ng/mL
51–55 years		87–238 µg/L	87–238 ng/mL
56–60 years		81–225 µg/L	81–225 ng/mL
61–65 years		75–212 µg/L	75–212 ng/mL
66–70 years		69–200 µg/L	69–200 ng/mL
71–75 years		64–188 µg/L	64–188 ng/mL
76–80 years		59–177 µg/L	59–177 ng/mL
81–85 years		55–166 µg/L	55–166 ng/mL
Somatostatin	P	<25 ng/L	<25 pg/mL
Testosterone, free			

(continued)

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Female, adult	S	10.4–65.9 pmol/L	3–19 pg/mL
Male, adult		312–1041 pmol/L	90–300 pg/mL
Testosterone, total,	S		
Female		0.21–2.98 nmol/L	6–86 ng/dL
Male		9.36–37.10 nmol/L	270–1070 ng/dL
Thyroglobulin	S	13–318 µg/L	1.3–31.8 ng/mL
Thyroid-binding globulin	S	13–30 mg/L	1.3–3.0 mg/dL
Thyroid-stimulating hormone (thyrotropin)	S	0.34–4.25 mIU/L	0.34–4.25 µIU/mL
Thyrotropin receptor antibody	S	≤1.75 IU/L	≤1.75 mIU/mL
Thyroxine, free (fT ₄)	S	9.0–16 pmol/L	0.7–1.24 ng/dL
Thyroxine, total (T ₄)	S	70–151 nmol/L	5.4–11.7 µg/dL
Thyroxine index (free)	S	6.7–10.9	6.7–10.9
Tissue transglutaminase (tTG) antibody, IgA	S		
Negative		<4.0 U/mL	<4.0 U/mL
Weak positive		4.0–10.0 U/mL	4.0–10.0 U/mL
Positive		>10.0 U/mL	>10.0 U/mL
Tissue transglutaminase (tTG) antibody, IgG	S		
Negative		<6.0 U/mL	<6.0 U/mL
Weak positive		6.0–9.0 U/mL	6.0–9.0 U/mL
Positive		>9.0 U/mL	>9.0 U/mL
Transferrin	S	2.0–4.0 g/L	200–400 mg/dL
Transferrin, carbohydrate deficient, for alcohol use	S	0.017	1.7%
Triglycerides	S	0.34–2.26 mmol/L	30–200 mg/dL
Triiodothyronine, free (fT ₃)	S	3.7–6.5 pmol/L	2.4–4.2 pg/mL
Triiodothyronine, total (T ₃)	S	1.2–2.1 nmol/L	77–135 ng/dL
Troponin I	S, P		
99th percentile of a healthy population		Method-dependent	Method-dependent
Troponin T	S, P		
99th percentile of a healthy population		0–14 ng/L	0–14 ng/L
Urea nitrogen	S	2.5–7.1 mmol/L	7–20 mg/dL
Uric acid	S		
Female		0.15–0.33 mmol/L	2.5–5.6 mg/dL
Male		0.18–0.41 mmol/L	3.1–7.0 mg/dL
Vasoactive intestinal polypeptide	P	0–60 ng/L	0–60 pg/mL
Zinc protoporphyrin (ZPP)	WB	0–400 µg/L	0–40 µg/dL
ZPP-to-heme ratio	WB	0–69 µmol ZPP/mol heme	0–69 µmol ZPP/mol heme

Abbreviations: AMF, amniotic fluid; BCE, bone collagen equivalent; P, plasma; S, serum; WB, whole blood.
Source: NJ Stone et al: J Am Coll Cardiol 63:2889–2934, 2014.

TABLE 3
TOXICOLOGY AND THERAPEUTIC DRUG MONITORING

DRUG	THERAPEUTIC RANGE		TOXIC LEVEL	
	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Acetaminophen	66–199 µmol/L	10–30 µg/mL	>1320 µmol/L	>200 µg/mL
Amikacin				
Peak	34–51 µmol/L	20–30 µg/mL	>60 µmol/L	>35 µg/mL
Trough	0–17 µmol/L	0–10 µg/mL	>17 µmol/L	>10 µg/mL
Amitriptyline/nortriptyline (total drug)	430–900 nmol/L	120–250 ng/mL	>1800 nmol/L	>500 ng/mL
Amphetamine	150–220 nmol/L	20–30 ng/mL	>1500 nmol/L	>200 ng/mL
Bromide	9.4–18.7 mmol/L	75–150 mg/dL	>18.8 mmol/L	>150 mg/dL
Mild toxicity			6.4–18.8 mmol/L	51–150 mg/dL
Severe toxicity			>18.8 mmol/L	>150 mg/dL
Lethal			>37.5 mmol/L	>300 mg/dL
Caffeine	25.8–103 µmol/L	5–20 µg/ml	>206 µmol/L	>40 µg/mL
Carbamazepine	17–42 µmol/L	4–10 µg/mL	> 85 µmol/L	>20 µg/mL
Chloramphenicol				
Peak	31–62 µmol/L	10–20 µg/mL	>77 µmol/L	>25 µg/mL
Trough	15–31 µmol/L	5–10 µg/mL	>46 µmol/L	>15 µg/mL
Chlordiazepoxide	1.7–10 µmol/L	0.5–3.0 µg/mL	>17 µmol/L	>5.0 µg/mL
Clonazepam	32–240 nmol/L	10–75 ng/mL	>320 nmol/L	>100 ng/mL
Clozapine	0.6–2.1 µmol/L	200–700 ng/mL	>3.7 µmol/L	>1200 ng/mL
Cocaine			>3.3 µmol/L	>1.0 µg/mL
Codeine	43–110 nmol/mL	13–33 ng/mL	>3700 nmol/mL	>1100 ng/mL (lethal)
Cyclosporine				
Renal transplant				
0–6 months	208–312 nmol/L	250–375 ng/mL	>312 nmol/L	>375 ng/mL
6–12 months after transplant	166–250 nmol/L	200–300 ng/mL	>250 nmol/L	>300 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	>150 ng/mL
Cardiac transplant				
0–6 months	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
6–12 months after transplant	125–208 nmol/L	150–250 ng/mL	>208 nmol/L	>250 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	150 ng/mL
Lung transplant				
0–6 months	250–374 nmol/L	300–450 ng/mL	>374 nmol/L	>450 ng/mL
Liver transplant				
Initiation	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
Maintenance	83–166 nmol/L	100–200 ng/mL	>166 nmol/L	>200 ng/mL
Desipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Diazepam (and metabolite)				
Diazepam	0.7–3.5 µmol/L	0.2–1.0 µg/mL	>7.0 µmol/L	>2.0 µg/mL
Nordiazepam	0.4– 6.6 µmol/L	0.1–1.8 µg/mL	>9.2 µmol/L	>2.5 µg/mL
Digoxin	0.64–1.6 nmol/L	0.5–1.2 ng/mL	>3.1 nmol/L	>2.4 ng/mL

(continued)

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (CONTINUED)				
DRUG	THERAPEUTIC RANGE		TOXIC LEVEL	
	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Disopyramide	5.3–14.7 µmol/L	2–5 µg/mL	>20.6 µmol/L	>7 µg/mL
Doxepin and nordoxepin				
Doxepin	0.36–0.98 µmol/L	101–274 ng/mL	>1.8 µmol/L	>503 ng/mL
Nordoxepin	0.38–1.04 µmol/L	106–291 ng/mL	>1.9 µmol/L	>531 ng/mL
Ethanol				
Behavioral changes			>4.3 mmol/L	>20 mg/dL
Legal limit			≥17 mmol/L	≥80 mg/dL
Critical with acute exposure			>54 mmol/L	>250 mg/dL
Ethylene glycol				
Toxic			>2 mmol/L	>12 mg/dL
Lethal			>20 mmol/L	>120 mg/dL
Ethosuximide	280–700 µmol/L	40–100 µg/mL	>700 µmol/L	>100 µg/mL
Everolimus (trough)				
Kidney transplant	3.1–8.34 nmol/L	3–8 ng/mL	>12.5 nmol/L	>12 ng/mL
Oncology	5.2–10.4 nmol/L	5.0–10.0 ng/mL	>12.5 nmol/L	>12 ng/mL
Felbamate (trough)	126–252 µmol/L	30–60 µg/mL	Toxic range not well established	
Flecainide	0.5–2.4 µmol/L	0.2–1.0 µg/mL	>3.6 µmol/L	>1.5 µg/mL
Gabapentin (trough)	11.7–116.8 µmol/L	2–20 µg/mL	Toxic range not well established	
Gentamicin				
Peak	10–21 µmol/mL	5–10 µg/mL	>25 µmol/mL	>12 µg/mL
Trough	0–4.2 µmol/mL	0–2 µg/mL	>4.2 µmol/mL	>2 µg/mL
Heroin (diacetyl morphine)			>700 µmol/L	>200 ng/mL (as morphine)
Ibuprofen	49–243 µmol/L	10–50 µg/mL	>970 µmol/L	>200 µg/mL
Imipramine (and metabolites)				
Desimipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Total imipramine + desimipramine	563–1130 nmol/L	150–300 ng/mL	>1880 nmol/L	>500 ng/mL
Isopropanol			>8.3 mmol/L	>50 mg/dL
Lamotrigine	11.7–54.7 µmol/L	3–14 µg/mL	>58.7 µmol/L	>15 µg/mL
Levetiracetam (Keppra)	29–176 µmol/L	5–30 µg/mL	Toxic range not well established	
Lidocaine	5.1–21.3 µmol/L	1.2–5.0 µg/mL	>38.4 µmol/L	>9.0 µg/mL
Lithium	0.5–1.3 mmol/L	0.5–1.3 meq/L	>2 mmol/L	>2 meq/L
Methadone	1.0–3.2 µmol/L	0.3–1.0 µg/mL	>6.5 µmol/L	>2 µg/mL
Methamphetamine	0.07–0.34 µmol/L	0.01–0.05 µg/mL	>3.35 µmol/L	>0.5 µg/mL
Methanol			>6 mmol/L	>20 mg/dL
Methotrexate				
Low-dose	0.01–0.1 µmol/L	0.01–0.1 µmol/L	>0.1 µmol/L	>0.1 µmol/L
High-dose (24 h)	<5.0 µmol/L	<5.0 µmol/L	>5.0 µmol/L	>5.0 µmol/L
High-dose (48 h)	<0.50 µmol/L	<0.50 µmol/L	>0.5 µmol/L	>0.5 µmol/L
High-dose (72 h)	<0.10 µmol/L	<0.10 µmol/L	>0.1 µmol/L	>0.1 µmol/L

TABLE 3
TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (CONTINUED)

DRUG	THERAPEUTIC RANGE		TOXIC LEVEL	
	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Morphine	232–286 µmol/L	65–80 ng/mL	>720 µmol/L	>200 ng/mL
Mycophenolic acid	3.1–10.9 µmol/L	1.0–3.5 ng/mL	>37 µmol/L	>12 ng/mL
Nitroprusside (as thiocyanate)	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nortriptyline	190–569 nmol/L	50–150 ng/mL	>1900 nmol/L	>500 ng/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>258 µmol/L	>60 µg/mL
Phenytoin	40–79 µmol/L	10–20 µg/mL	>158 µmol/L	>40 µg/mL
Phenytoin, free	4.0–7.9 µg/mL	1–2 µg/mL	>13.9 µg/mL	>3.5 µg/mL
% Free	0.08–0.14	8–14%		
Primidone and metabolite				
Primidone	23–55 µmol/L	5–12 µg/mL	>69 µmol/L	>15 µg/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>215 µmol/L	>50 µg/mL
Procainamide				
Procainamide	17–42 µmol/L	4–10 µg/mL	>43 µmol/L	>10 µg/mL
NAPA (N-acetylprocainamide)	22–72 µmol/L	6–20 µg/mL	>126 µmol/L	>35 µg/mL
Quinidine	6.2–15.4 µmol/L	2.0–5.0 µg/mL	>19 µmol/L	>6 µg/mL
Salicylates	145–2100 µmol/L	2–29 mg/dL	>2900 µmol/L	>40 mg/dL
Sirolimus (trough level)				
Kidney transplant	4.4–15.4 nmol/L	4–14 ng/mL	>16 nmol/L	>15 ng/mL
Tacrolimus (FK506) (trough)				
Kidney and liver transplant				
Initiation	12–19 nmol/L	10–15 ng/mL	>25 nmol/L	>20 ng/mL
Maintenance	6–12 nmol/L	5–10 ng/mL	>25 nmol/L	>20 ng/mL
Heart transplant				
Initiation	19–25 nmol/L	15–20 ng/mL		
Maintenance	6–12 nmol/L	5–10 ng/mL		
Theophylline	56–111 µg/mL	10–20 µg/mL	>168 µg/mL	>30 µg/mL
Thiocyanate				
After nitroprusside infusion	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nonsmoker	17–69 µmol/L	1–4 µg/mL		
Smoker	52–206 µmol/L	3–12 µg/mL		
Tobramycin				
Peak	11–22 µg/L	5–10 µg/mL	>26 µg/L	>12 µg/mL
Trough	0–4.3 µg/L	0–2 µg/mL	>4.3 µg/L	>2 µg/mL
Topiramate (trough)	5.9–58.9 µmol/L	2.0–20.0 µg/mL	Toxic range not well established	
Valproic acid	346–693 µmol/L	50–100 µg/mL	>693 µmol/L	>100 µg/mL
Vancomycin				
Peak	14–28 µmol/L	20–40 µg/mL	>55 µmol/L	>80 µg/mL
Trough	3.5–10.4 µmol/L	5–15 µg/mL	>14 µmol/L	>20 µg/mL
Zonisamide (trough)	47–188 µmol/L	10–40 µg/mL	Toxic range not well established	

TABLE 4
VITAMINS AND SELECTED TRACE MINERALS

SPECIMEN	ANALYTE	REFERENCE RANGE	
		SI UNITS	CONVENTIONAL UNITS
Aluminum	S	<0.2 µmol/L	<5.41 µg/L
Arsenic	WB	0.0–0.17 µmol/L	0–13 µg/L
Cadmium	WB	<44.5 nmol/L	<5.0 µg/L
Coenzyme Q10 (ubiquinone)	P	433–1532 µg/L	433–1532 µg/L
β-Carotene	S	0.07–1.43 µmol/L	4–77 µg/dL
Copper	S	11–22 µmol/L	70–140 µg/dL
Folic acid	RC	340–1020 nmol/L cells	150–450 ng/mL cells
Folic acid	S	12.2–40.8 nmol/L	5.4–18.0 ng/mL
Lead	S		
Adult		<0.5 µmol/L	<10 µg/dL
Children		<0.25 µmol/L	<5 µg/dL
Mercury	WB	0–50 µmol/L	0–10 µg/L
Selenium	S	0.8–2.0 µmol/L	63–160 µg/L
Vitamin A	S	0.7–3.5 µmol/L	20–100 µg/dL
Vitamin B ₁ (thiamine)	S	0–75 nmol/L	0–2 µg/dL
Vitamin B ₂ (ribof avin)	S	106–638 nmol/L	4–24 µg/dL
Vitamin B ₆	P	20–121 nmol/L	5–30 ng/mL
Vitamin B ₁₂	S	206–735 pmol/L	279–996 pg/mL
Vitamin C (ascorbic acid)	S	23–57 µmol/L	0.4–1.0 mg/dL
Vitamin D 1,25-dihydroxy, total	S, P	36–180 pmol/L	15–75 pg/mL
Vitamin D 25-hydroxy, total	P	75–250 nmol/L	30–100 ng/mL
Vitamin E	S	12–42 µmol/L	5–18 µg/mL
Vitamin K	S	0.29–2.64 nmol/L	0.13–1.19 ng/mL
Zinc	S	11.5–18.4 µmol/L	75–120 µg/dL

Abbreviations: P, plasma; RC, red cells; S, serum; WB, whole blood.

TABLE 5
CEREBROSPINAL FLUID^a

CONSTITUENT	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Osmolarity	292–297 mmol/kg water	292–297 mOsm/L
Electrolytes		
Sodium	137–145 mmol/L	137–145 meq/L
Potassium	2.7–3.9 mmol/L	2.7–3.9 meq/L
Calcium	1.0–1.5 mmol/L	2.1–3.0 meq/L
Magnesium	1.0–1.2 mmol/L	2.0–2.5 meq/L
Chloride	116–122 mmol/L	116–122 meq/L
CO ₂ content	20–24 mmol/L	20–24 meq/L
P _{co2}	6–7 kPa	45–49 mmHg
pH	7.31–7.34	
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein:		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index ^b	0.29–0.59	
Oligoclonal bands (OGB)	<2 bands not present in matched serum sample	
Ammonia	15–47 μmol/L	25–80 μg/dL
Creatinine	44–168 μmol/L	0.5–1.9 mg/dL
Myelin basic protein	<4 μg/L	
Cerebrospinal fluid pressure		50–180 mmH ₂ O
Cerebrospinal fluid volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per μL	
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

^aSince cerebrospinal fluid (CSF) concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fluctuate rapidly (such as plasma glucose) may not achieve stable values until after a significant lag phase. ^bIgG index = CSF IgG (mg/dL) × serum albumin (g/dL)/serum IgG (g/dL) × CSF albumin (mg/dL).

TABLE 6
URINE ANALYSIS AND RENAL FUNCTION TESTS

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Acidity, titratable	20–40 mmol/d	20–40 meq/d
Aldosterone	Normal diet: 6–25 µg/d	Normal diet: 6–25 µg/d
	Low-salt diet: 17–44 µg/d	Low-salt diet: 17–44 µg/d
	High-salt diet: 0–6 µg/d	High-salt diet: 0–6 µg/d
Aluminum	0.19–1.11 µmol/L	5–30 µg/L
Ammonia	30–50 mmol/d	30–50 meq/d
Amylase		4–400 U/L
Amylase/creatinine clearance ratio ($[Cl_{am}/Cl_{cr}] \times 100$)	1–5	1–5
Arsenic	0.07–0.67 µmol/d	5–50 µg/d
Bence Jones protein, urine, qualitative	Not applicable	None detected
Bence Jones protein, urine, quantitative		
Free kappa	1.4–24.2 mg/L	0.14–2.42 mg/dL
Free lambda	0.2–6.7 mg/L	0.02–0.67 mg/dL
K/L ratio	2.04–10.37	2.04–10.37
Calcium (10 meq/d or 200 mg/d dietary calcium)	<7.5 mmol/d	<300 mg/d
Chloride	140–250 mmol/d	140–250 mmol/d
Citrate	320–1240 mg/d	320–1240 mg/d
Copper	<0.95 µmol/d	<60 µg/d
Coproporphyrins (types I and III)	0–20 µmol/mol creatinine	0–20 µmol/mol creatinine
Cortisol, free	55–193 nmol/d	20–70 µg/d
Creatine, as creatinine		
Female	<760 µmol/d	<100 mg/d
Male	<380 µmol/d	<50 mg/d
Creatinine	8.8–14 mmol/d	1.0–1.6 g/d
Dopamine	392–2876 nmol/d	60–440 µg/d
Eosinophils	<100 eosinophils/mL	<100 eosinophils/mL
Epinephrine	0–109 nmol/d	0–20 µg/d
Glomerular filtration rate	>60 mL/min/1.73 m ² For African Americans, multiply the result by 1.21	>60 mL/min/1.73 m ² For African Americans, multiply the result by 1.21
Glucose (glucose oxidase method)	0.3–1.7 mmol/d	50–300 mg/d
5-Hydroindoleacetic acid (5-HIAA)	0–78.8 µmol/d	0–15 mg/d
Hydroxyproline	53–328 µmol/d	53–328 µmol/d
Iodine, spot urine		
WHO classification of iodine deficiency:		
Not iodine deficient	>100 µg/L	>100 µg/L
Mild iodine deficiency	50–100 µg/L	50–100 µg/L
Moderate iodine deficiency	20–49 µg/L	20–49 µg/L
Severe iodine deficiency	<20 µg/L	<20 µg/L
Ketone (acetone)	Negative	Negative
17 Ketosteroids	3–12 mg/d	3–12 mg/d

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS (CONTINUED)		
	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Metanephrines		
Metanephrine	30–350 µg/d	30–350 µg/d
Normetanephrine	50–650 µg/d	50–650 µg/d
Microalbumin		
Normal	0.0–0.03 g/d	0–30 mg/d
Microalbuminuria	0.03–0.30 g/d	30–300 mg/d
Clinical albuminuria	>0.3 g/d	>300 mg/d
Microalbumin/creatinine ratio		
Normal	0–3.4 g/mol creatinine	0–30 µg/mg creatinine
Microalbuminuria	3.4–34 g/mol creatinine	30–300 µg/mg creatinine
Clinical albuminuria	>34 g/mol creatinine	>300 µg/mg creatinine
β ₂ -Microglobulin	0–160 µg/L	0–160 µg/L
Norepinephrine	89–473 nmol/d	15–80 µg/d
N-telopeptide (cross-linked), NTx		
Female, premenopausal	17–94 nmol BCE/mmol creatinine	17–94 nmol BCE/mmol creatinine
Female, postmenopausal	26–124 nmol BCE/mmol creatinine	26–124 nmol BCE/mmol creatinine
Male	21–83 nmol BCE/mmol creatinine	21–83 nmol BCE/mmol creatinine
Osmolality	100–800 mosm/kg	100–800 mosm/kg
Oxalate		
Male	80–500 µmol/d	7–44 mg/d
Female	45–350 µmol/d	4–31 mg/d
pH	5.0–9.0	5.0–9.0
Phosphate (phosphorus) (varies with intake)	12.9–42.0 mmol/d	400–1300 mg/d
Porphobilinogen	None	None
Potassium (varies with intake)	25–100 mmol/d	25–100 meq/d
Protein	<0.15 g/d	<150 mg/d
Protein/creatinine ratio	Male: 15–68 mg/g Female: 10–107 mg/g	Male: 15–68 mg/g Female: 10–107 mg/g
Sediment		
Red blood cells	0–2/high-power field	
White blood cells	0–2/high-power field	
Bacteria	None	
Crystals	None	
Bladder cells	None	
Squamous cells	None	
Tubular cells	None	
Broad casts	None	
Epithelial cell casts	None	
Granular casts	None	

(continued)

TABLE 6
URINE ANALYSIS AND RENAL FUNCTION TESTS (CONTINUED)

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Hyaline casts	0–5/low-power field	
Red blood cell casts	None	
Waxy casts	None	
White cell casts	None	
Sodium (varies with intake)	100–260 mmol/d	100–260 meq/d
Specific gravity:		
After 12-h fluid restriction	>1.025	>1.025
After 12-h deliberate water intake	≤1.003	≤1.003
Tubular reabsorption, phosphorus	0.79–0.94 of filtered load	79–94% of filtered load
Urea nitrogen	214–607 mmol/d	6–17 g/d
Uric acid (normal diet)	1.49–4.76 mmol/d	250–800 mg/d
Vanillylmandelic acid (VMA)	<30 μmol/d	<6 mg/d

Abbreviation: BCE, bone collagen equivalent.

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REVIEW AND SELF-ASSESSMENT*

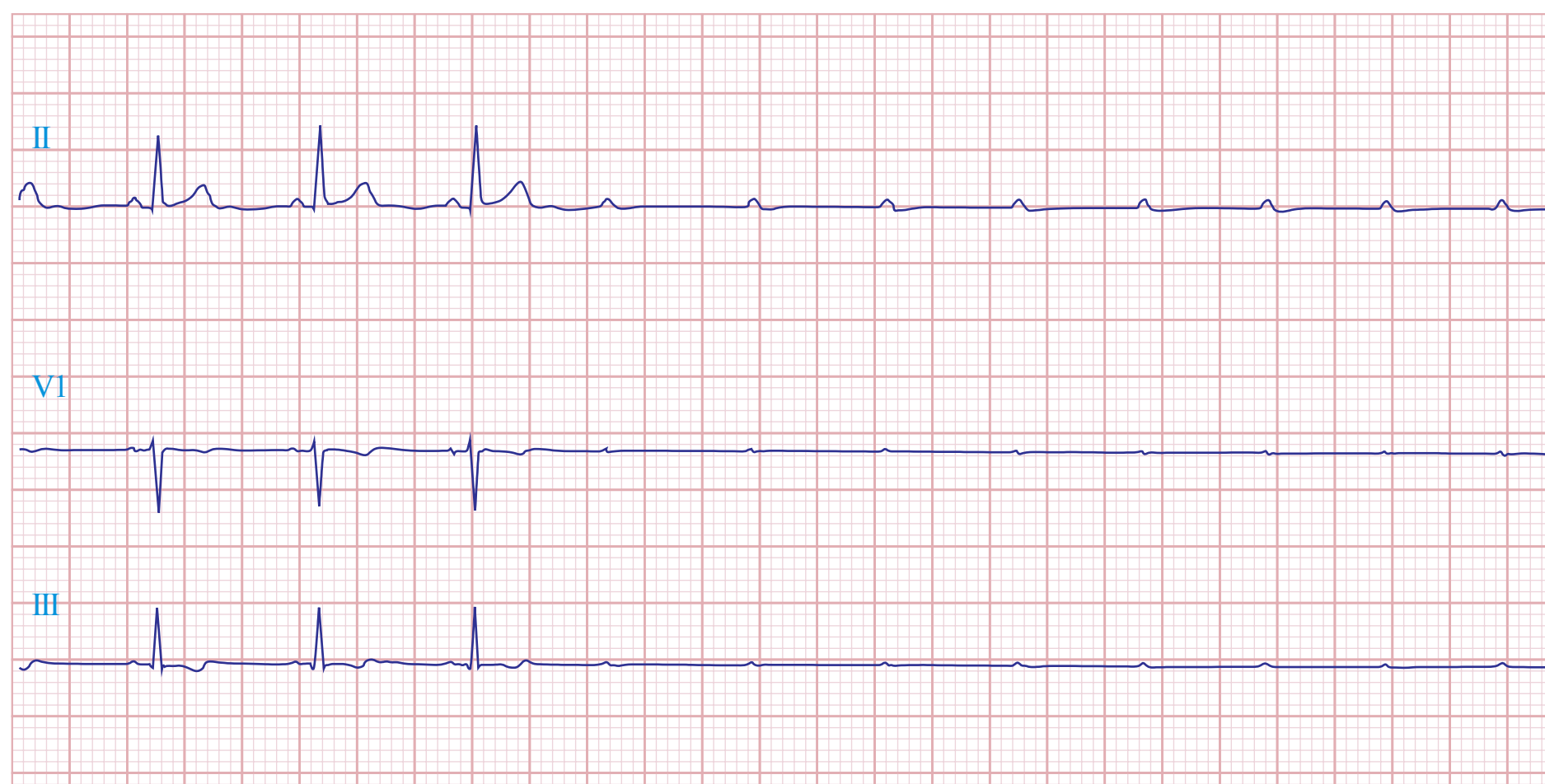
Charles M. Wiener ■ Cynthia D. Brown ■ Brian Houston

QUESTIONS

DIRECTIONS: Choose the **one best** response to each question.

1. You are appointed as a cardiac epidemiologist advisor on an international committee setting global health policy. Your committee is assigned to predict health trends in a Pacific East Asian nation with a population and environment very similar to China. At this point in history, the nation is just moving from the first classic stage in the epidemiologic transition (“pestilence and famine”) to the second classic stage (“receding pandemics”). In regard to the anticipated patterns of cardiovascular disease (CVD) in this nation, which of the following is true?
 - A. As this nation enters the stage of receding pandemics, you would expect the majority of CVD morbidity and mortality to be due to cardiomyopathies secondary to infectious agents.
 - B. Each nation or geographical location progresses through the five stages of epidemiologic transition identically in regard to CVD risk.
 - C. In this nation, when CVD mortality peaks, you would expect stroke mortality to be greater than coronary heart disease mortality.
 - D. One would expect a very homogeneous epidemiologic pattern of CVD risk throughout this nation over time.
 - E. You anticipate that CVD mortality will inexorably climb as this nation progresses through the five stages of the epidemiologic transition.
2. You are working in a rural health clinic in Northern India. You evaluate an 8-year-old boy who has never seen a physician. His mother tells you that he is unable to keep up with his peers in terms of physical activity. On your initial examination of his skin, you notice clubbing and cyanosis in his feet, but his hands appear normal. Without any further examination, you suspect that he has which of the following congenital abnormalities?
 - A. Atrial septal defect
 - B. Dextro-transposition of the great arteries (TGAs)
 - C. Patent ductus arteriosus with secondary pulmonary hypertension
 - D. Tetralogy of Fallot
 - E. Ventricular septal defect
3. A 55-year-old African American woman with no past medical history presents precipitously to the emergency department with syncope and the electrocardiogram (ECG) noted in Figure 1A. You also note painful subcutaneous nodules on her legs (similar to those shown in Figure 1B). You suspect that the cardiac and skin abnormalities are most likely due to:
 - A. Carney syndrome
 - B. Hypothyroidism
 - C. Sarcoidosis
 - D. Systemic lupus erythematosus
 - E. Tertiary syphilis

*Questions and answers were taken from Wiener CM, Brown CD, Houston B (eds). *Harrison's Self-Assessment and Board Review*, 19th ed. New York, McGraw-Hill, 2017.



A



B

FIGURE 1 Courtesy of Robert Swerlick, MD; with permission.

4. You are evaluating Mr. Estebez, a 67-year-old owner of a wildly successful chain of sushi restaurants. He complains of shortness of breath with exertion, lower extremity edema, and awakening at night feeling acutely short of breath. You wish to assess his volume status, and know that jugular venous pulse (JVP) assessment is the single most important physical examination measurement to aid you in this component of your evaluation. Which of the following statements regarding JVP measurement is true?
 - A. If done properly, the angle of inclination matters little to the measurement of JVP.
 - B. In normal patients, the JVP rises with inspiration due to the augmented volume loading of the right heart.
 - C. Measurement of the elevation of the top of the JVP and the sternal inflection point (angle of Louis) will provide a highly accurate measurement of central venous pressure.
 - D. The external jugular is preferred over the internal jugular vein due to its ease of visibility.
 - E. Venous pulsations above the clavicle in the sitting position are abnormal.

5. Which of the following statements regarding blood pressure measurements is true?
 - A. Systolic pressure increases and diastolic pressure decreases when measured in more distal arteries.
 - B. Systolic leg blood pressures are usually as much as 20 mmHg lower than arm blood pressures.
 - C. The concept of “white coat hypertension” (blood pressures measured in office or hospital settings significantly higher than in nonclinical settings) has been shown to be a myth.
 - D. The difference in blood pressure measured in both arms should be less than 20 mmHg.
 - E. Using a blood pressure cuff that is too small will result in a marked underestimation of the true blood pressure.
6. A 75-year-old man presents to your emergency department appearing quite ill. His family says he has not had his normal energy for the last 6 months, and they noted he was confused and lethargic for the last day or two. As you take a history from the family, you palpate the patient’s radial pulse and notice a regular beat-to-beat variability of pulse amplitude, although his rhythm is regular. Indeed, as you later take his blood pressure, you note that only every other phase I (systolic) Korotkoff sound is audible as the cuff pressure is slowly lowered and that this is independent of the respiratory cycle. Based on this, you suspect this patient has which of the following?
 - A. Atrial fibrillation
 - B. Cardiac tamponade
 - C. Constrictive pericarditis
 - D. Pulmonary embolism
 - E. Severe left ventricular dysfunction
7. A 78-year-old man is admitted to the intensive care unit with decompensated heart failure. He has longstanding ischemic cardiomyopathy. ECG shows atrial fibrillation and left bundle branch block. Chest radiograph shows cardiomegaly and bilateral alveolar infiltrates with Kerley B lines. Which of the following is least likely to be present on physical examination?
 - A. Fourth heart sound
 - B. Irregular heart rate
 - C. Kussmaul sign
 - D. Reversed splitting of the second heart sound
 - E. Third heart sound
8. A 24-year-old man is referred to cardiologist after an episode of syncope while playing basketball. He has no recollection of the event, but he was told that he collapsed while running. He awakened lying on the ground and suffered multiple contusions as a result of the fall. He has always been an active individual but recently has developed some chest pain with exertion that has caused him to restrict his activity. His father died at age 44 while rock climbing. He believes his father’s cause of death was sudden cardiac death and recalls being told his father had an enlarged heart. On examination, the patient has a III/VI mid-systolic crescendo-decrescendo murmur. His ECG shows evidence of left ventricular hypertrophy. You suspect hypertrophic cardiomyopathy as the cause of the patient’s heart disease. Which of the following maneuvers would be expected to cause an increase in the loudness of the murmur?
 - A. Handgrip exercise
 - B. Squatting
 - C. Standing
 - D. Valsalva maneuver
 - E. A and B
 - F. C and D
9. A 75-year-old woman with widely metastatic non–small-cell lung cancer is admitted to the intensive care unit with a systolic blood pressure of 73/52 mmHg. She presented complaining of fatigue and worsening dyspnea over the last 3–5 days. Her physical examination shows elevated neck veins. Chest radiograph shows a massive, water bottle-shaped heart shadow and no new pulmonary infiltrates. Which of the following additional findings is most likely present on physical examination?
 - A. Fall in systolic blood pressure >10 mmHg with inspiration
 - B. Lack of fall of the jugular venous pressure with inspiration
 - C. Late diastolic murmur with opening snap
 - D. Pulsus parvus et tardus
 - E. Rapid y-descent of jugular venous pressure tracing
10. Which of the following statements regarding normal depolarization patterns of the heart is true?
 - A. Each normal sinus beat is initiated by spontaneous depolarization in the atrioventricular (AV) node.
 - B. The normal order of depolarization is as follows: sinoatrial (SA) node – atrial myocardium – AV node – His bundle – Purkinje fibers – ventricular myocardium.
 - C. The right bundle branch bifurcates into an anterior and posterior fascicle.
 - D. The SA node is unique in its ability to spontaneously depolarize, a quality known as automaticity.
 - E. Within the ventricular myocardium, depolarization sweeps from epicardium to endocardium.
11. All of the following ECG waveforms are matched correctly to the cardiac cycle that they represent EXCEPT:
 - A. P wave – atrial repolarization
 - B. PR interval – atrial repolarization
 - C. QRS complex – ventricular depolarization
 - D. T wave – ventricular repolarization
 - E. U wave – ventricular repolarization

12. Which of the following mean QRS vectors in the frontal electrocardiographic plane is matched appropriately to its designation?

- A. -20 degrees – normal axis
- B. -35 degrees – right axis deviation
- C. 110 degrees – left axis deviation
- D. -80 degrees – extreme axis deviation
- E. All of the above are incorrect

13. Which of the following is represented in the ECG shown in Figure 2?

- A. First-degree heart block
- B. Left bundle branch block
- C. P-pulmonale
- D. Right bundle branch block
- E. S1Q3T3 (McGinn-White pattern) indicative of right ventricular strain

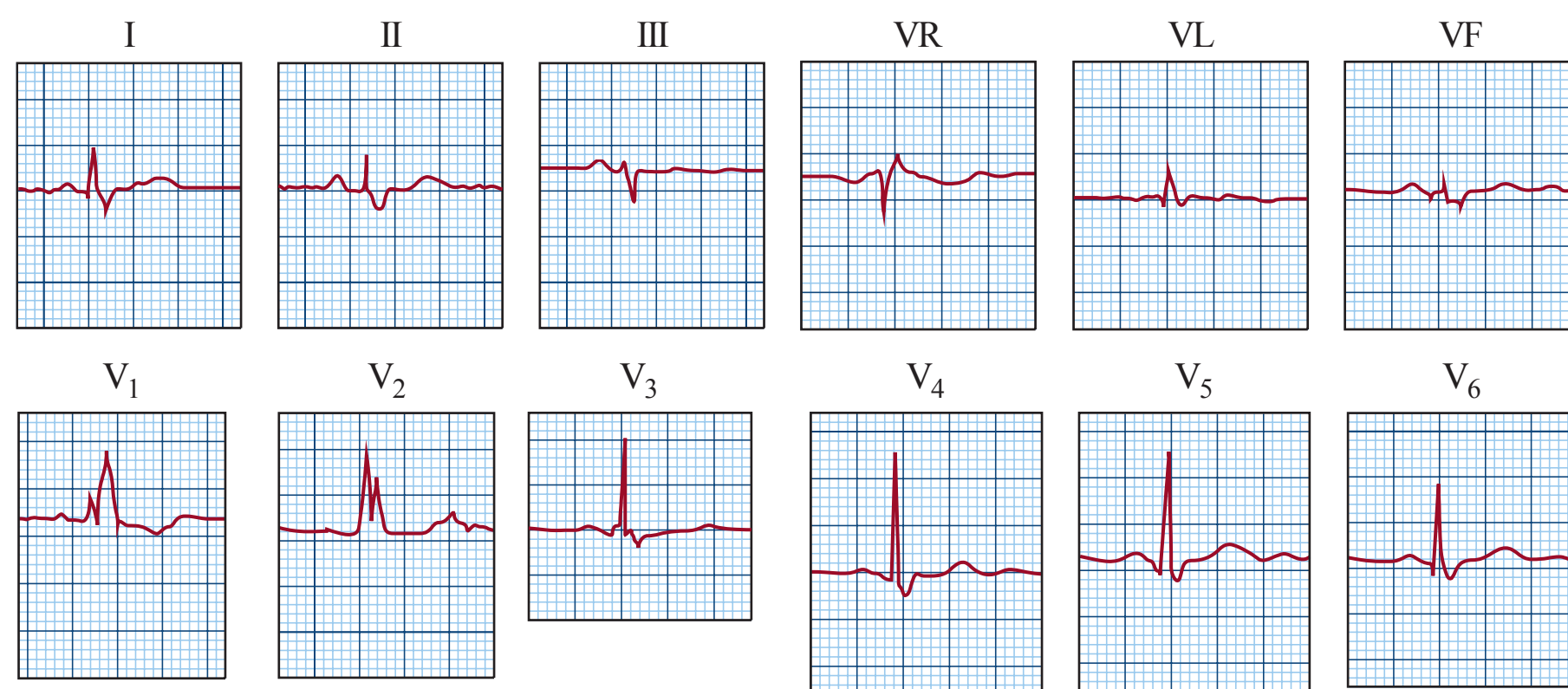


FIGURE 2 From Fuster V, Walsh R, Harrington R, et al (eds): *Hurst's The Heart*, 13th ed. New York, NY: McGraw-Hill, 2011, Fig. 15-31B.

14. Which of the following options describes the primary finding in the ECG shown in Figure 3?

- A. Left ventricular hypertrophy
- B. Normal ECG
- C. Peaked T waves, possibly hyperkalemia
- D. Sinus bradycardia
- E. ST elevation in the anterior precordial leads; suspect anterior myocardial ischemia

15. A 56-year-old construction worker with hypertension and a prior history of tobacco abuse presents to the emergency department with 30 minutes of acute-onset nausea, dyspnea, and chest pressure. His initial ECG is presented in Figure 4. All of the following are present in this ECG EXCEPT:

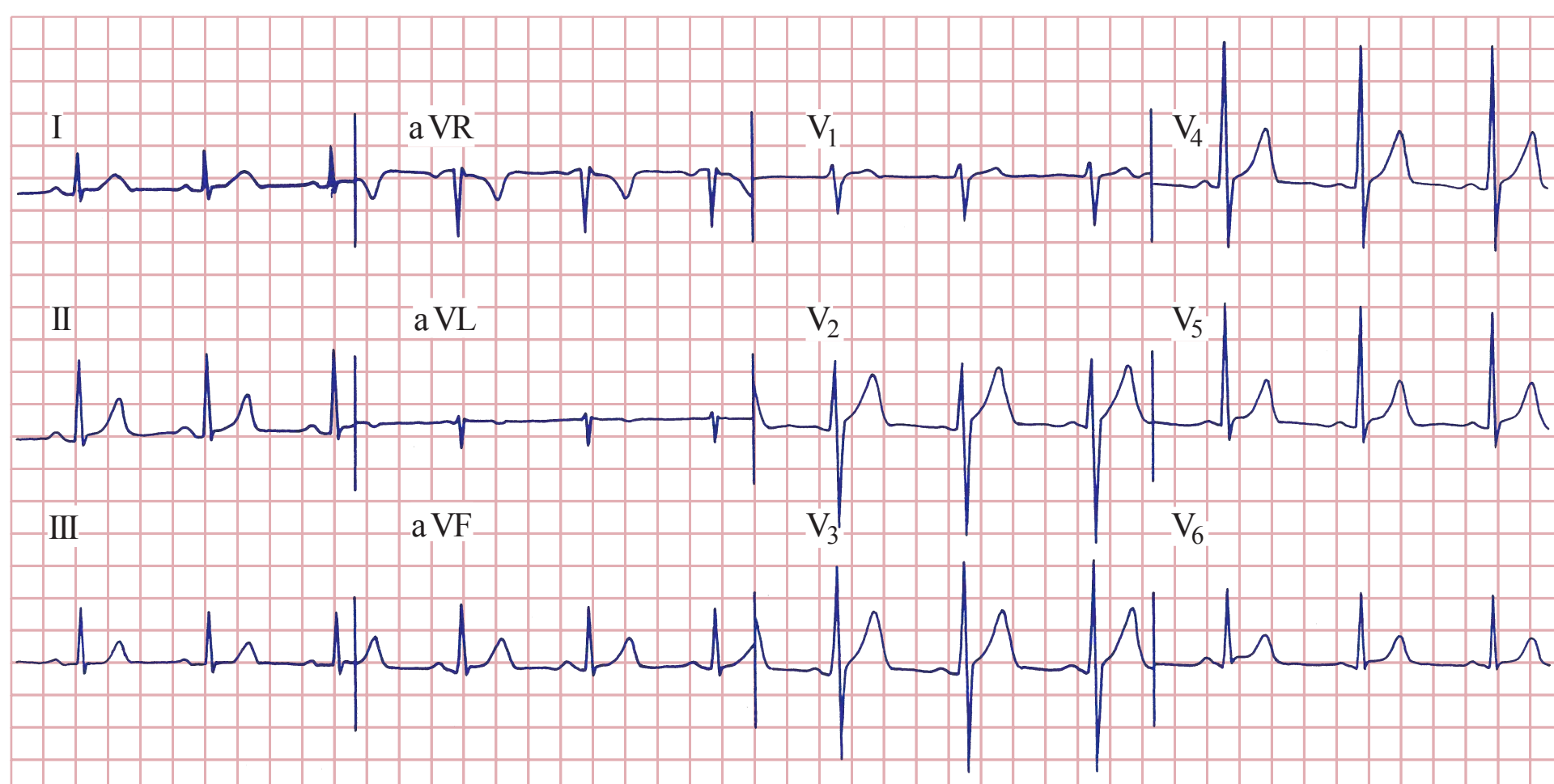


FIGURE 3

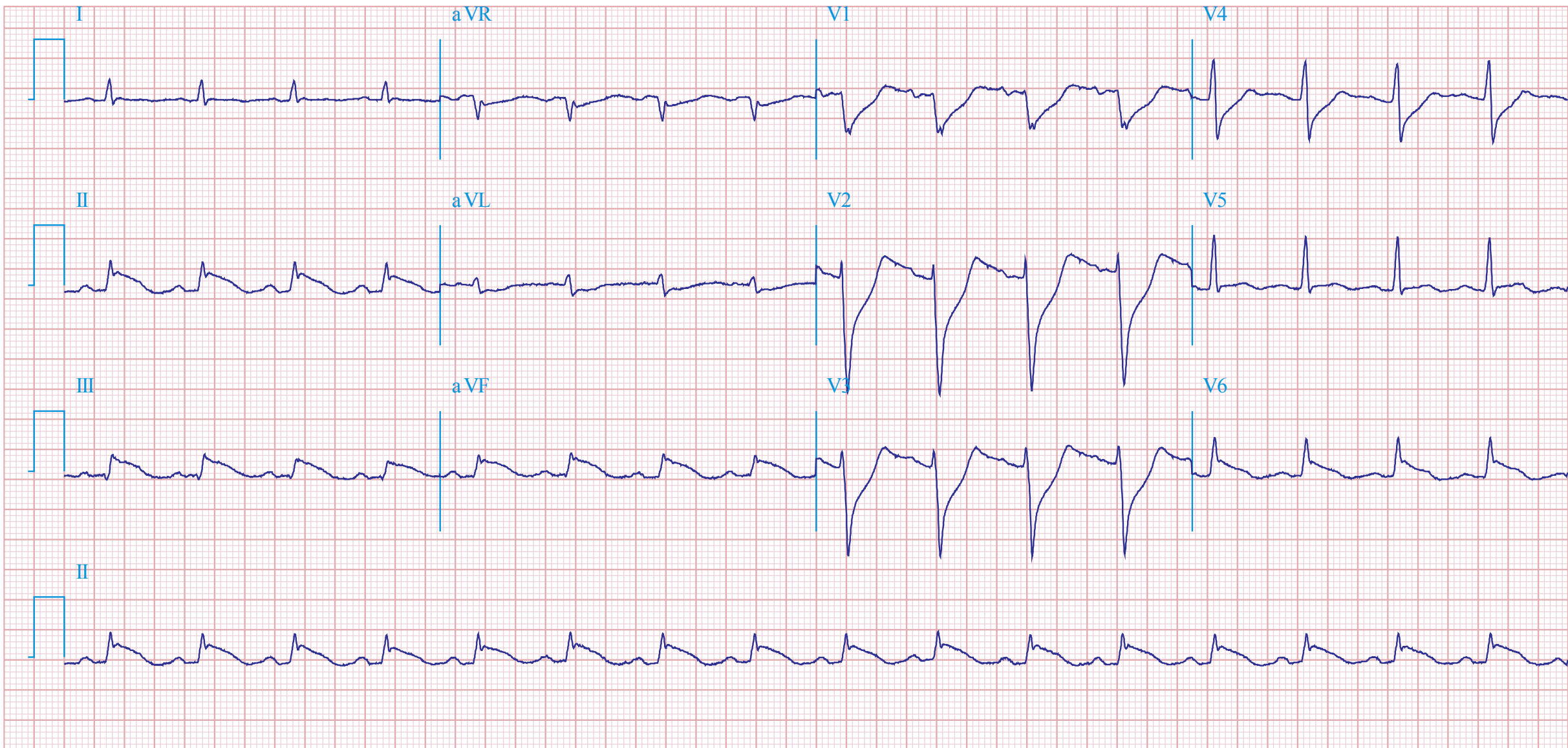


FIGURE 4

- A. Inferior myocardial ischemia
 B. P waves
 C. Posterior myocardial ischemia
 D. Sinus tachycardia
 E. Ventricular tachycardia
16. In the patient described in Question 15, which of the following coronary arteries is most likely occluded?
- A. First septal perforator
 B. Proximal left anterior descending artery
 C. Proximal left circumflex artery
 D. Proximal left anterior descending and left circumflex arteries
 E. Right coronary artery
17. A 48-year-old woman visits you in primary care clinic for initial evaluation after moving across the country. You have no past medical records, although she insists they were mailed a week prior. She states that she has had “some heart troubles,” but she is not clear on the details. Also, she is on pills for “cholesterol and blood pressure.” The initial ECG is shown in Figure 5. Which of the following statements regarding this ECG is true?
- A. It is likely she has suffered a prior myocardial infarction.
 B. She is in normal sinus rhythm.
 C. The presence of a left bundle branch block on this ECG indicates dyssynchronous mechanical contraction.
 D. The presence of premature ventricular contractions and tachycardia is concerning for electrolyte imbalance.
 E. The presence of anterior T-wave inversions is concerning in this ECG for acute myocardial ischemia.

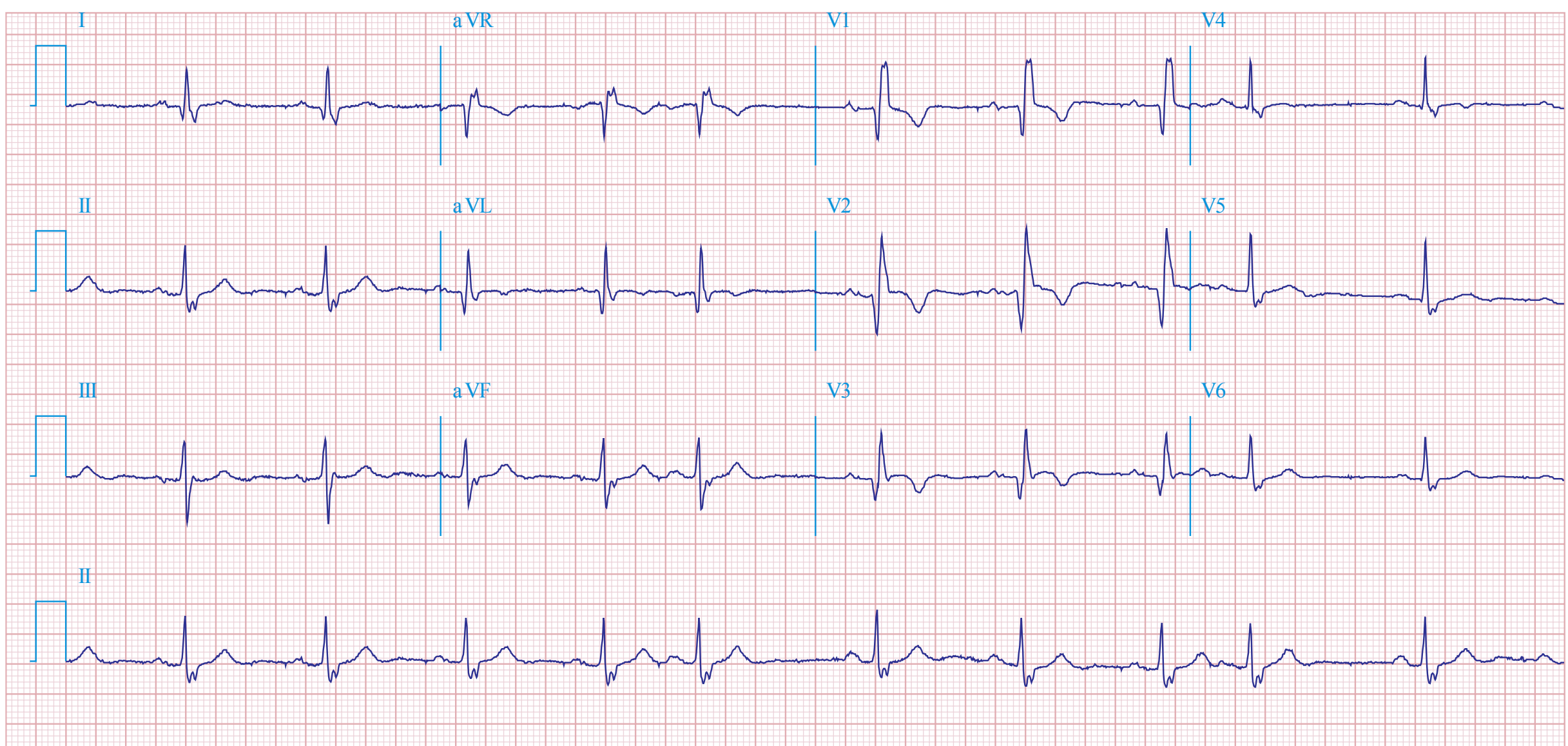


FIGURE 5

18. You are asked to evaluate a 27-year-old internal medicine resident reporting 1 week of cough, coryza, and a low-grade fever. Today, he has developed rapidly escalating chest discomfort while in clinic. He notes that the pain becomes more intense when he takes a deep breath. You perform a standard 12-lead ECG (see Figure 6). On examination, his blood pressure is normal, he is afebrile, and his jugular venous pulse is not elevated. However, he appears mildly uncomfortable

from the chest pain. The next most appropriate step would be which of the following?

- Administer aspirin, intravenous heparin, sublingual nitroglycerin, and clopidogrel.
- Emergently obtain transthoracic echocardiogram with possible pericardiocentesis.
- Emergently perform coronary angiography to evaluate for acute myocardial infarction.
- Prescribe ibuprofen and colchicine.
- Refer for treadmill stress test.

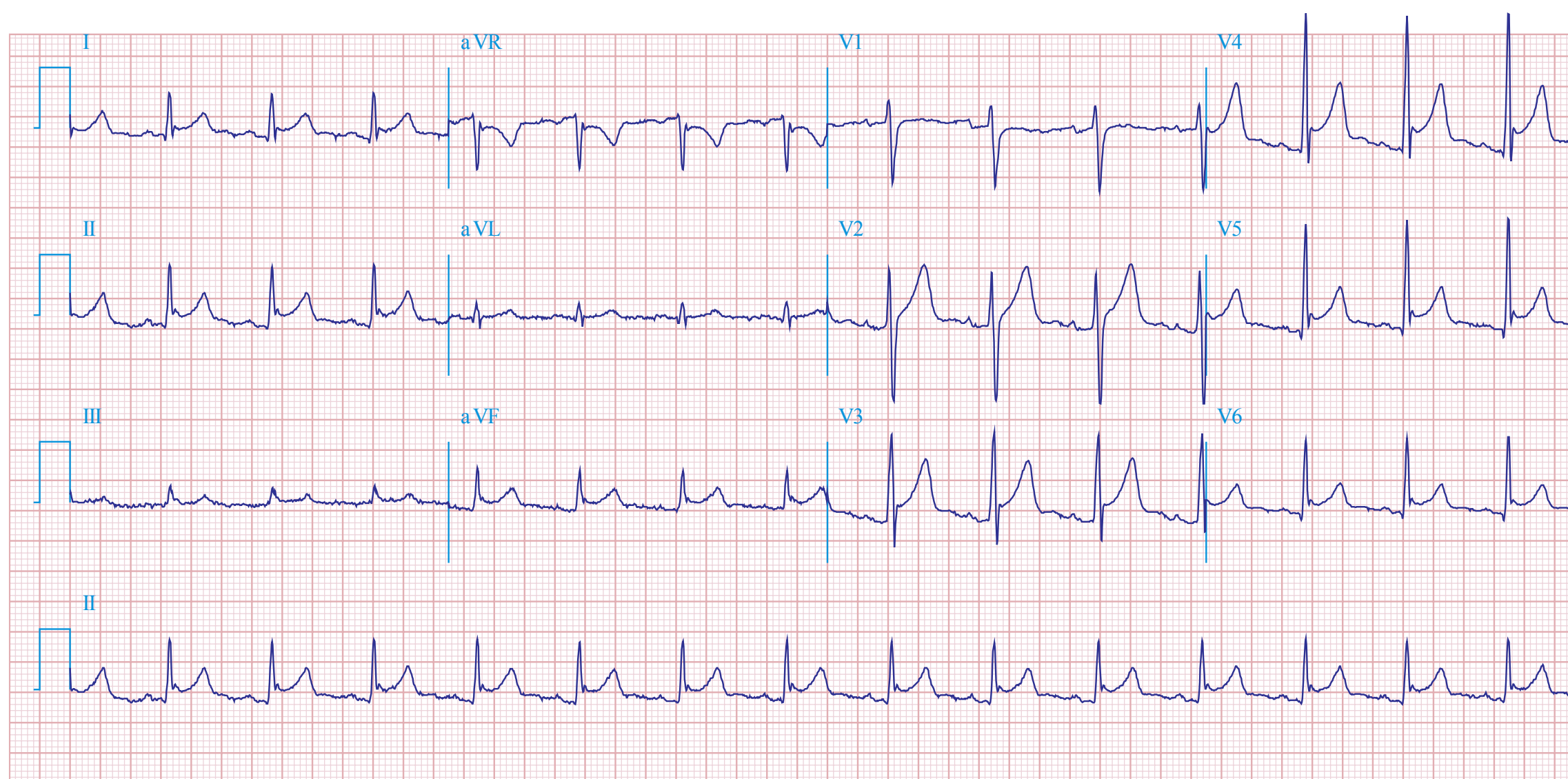


FIGURE 6

19. A large snowstorm hits your area on a Thursday, and the roads are largely impassible until the following Monday. On Monday morning, a 48-year-old man is brought by emergency medical services (EMS) to the emergency department after being found with altered mental status

by a neighbor. He is obtunded and unable to provide a history. You note a left brachial artery hemodialysis fistula in place. His initial ECG is shown in Figure 7. Which of the following electrolyte abnormalities would you expect to find in this patient?

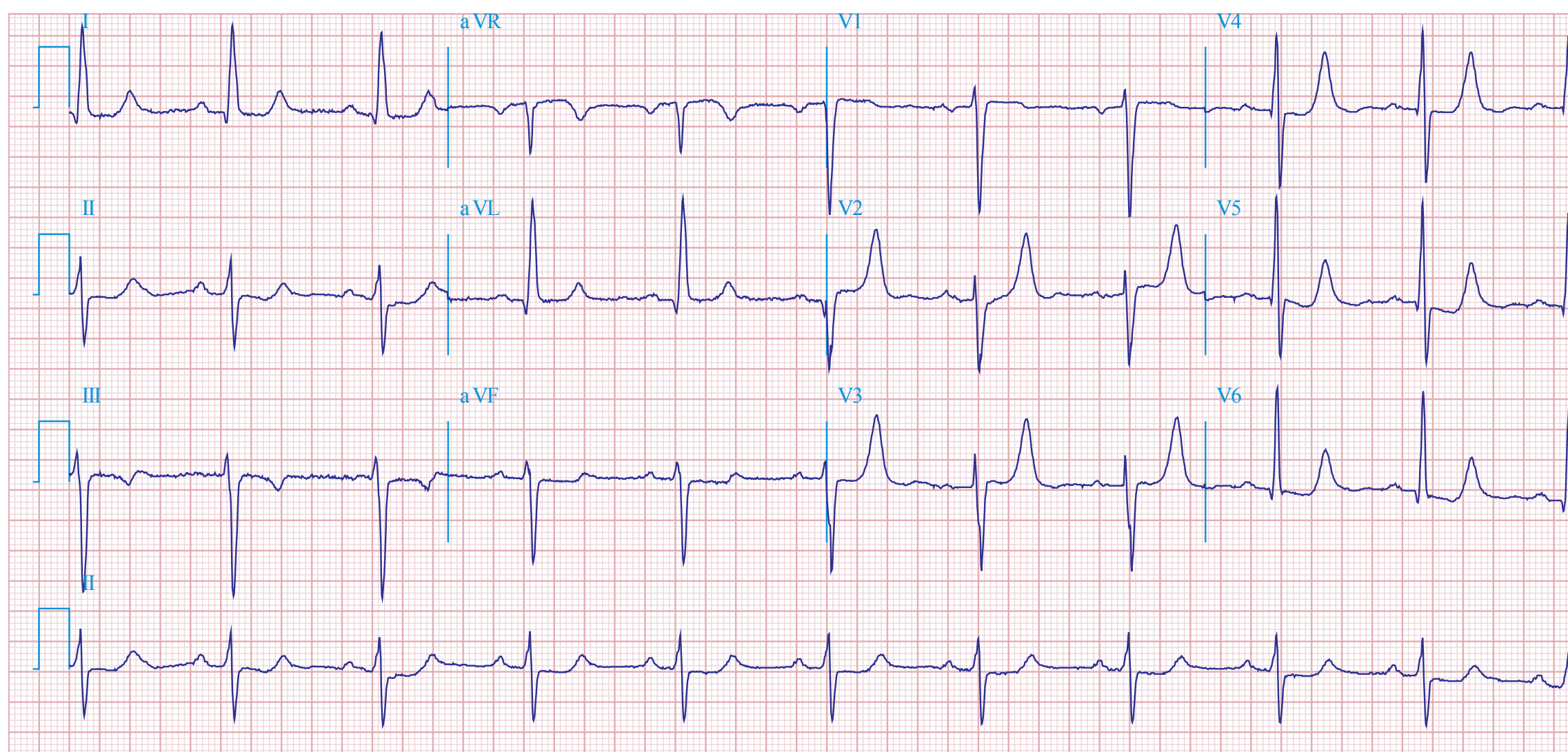


FIGURE 7

- A. Hypercalcemia
- B. Hyperkalemia
- C. Hypokalemia
- D. Hypomagnesemia
- E. Hyponatremia

20. A 66-year-old man is admitted to the hospital for progressive dyspnea on exertion and fatigue. He has a past medical history of tobacco abuse and is widely traveled, recently returning from a multicountry trip through South America. On presentation, his heart rate is 104 bpm and irregularly irregular. Blood pressure is 96/76 mmHg. You note

an elevated jugular venous pulsation and marked lower extremity edema. Echocardiogram reveals a left ventricular ejection fraction of 55%, and still images from his echocardiogram are shown in Figure 8. To elucidate the etiology of his heart failure, which of the following is the most appropriate diagnostic test to perform next?

- A. Bone marrow biopsy
- B. Genetic testing for transthyretin mutations
- C. Positron emission tomography cardiac stress test
- D. Serologies for *Trypanosoma cruzi*
- E. Serum and urine protein electrophoresis and light chain assay

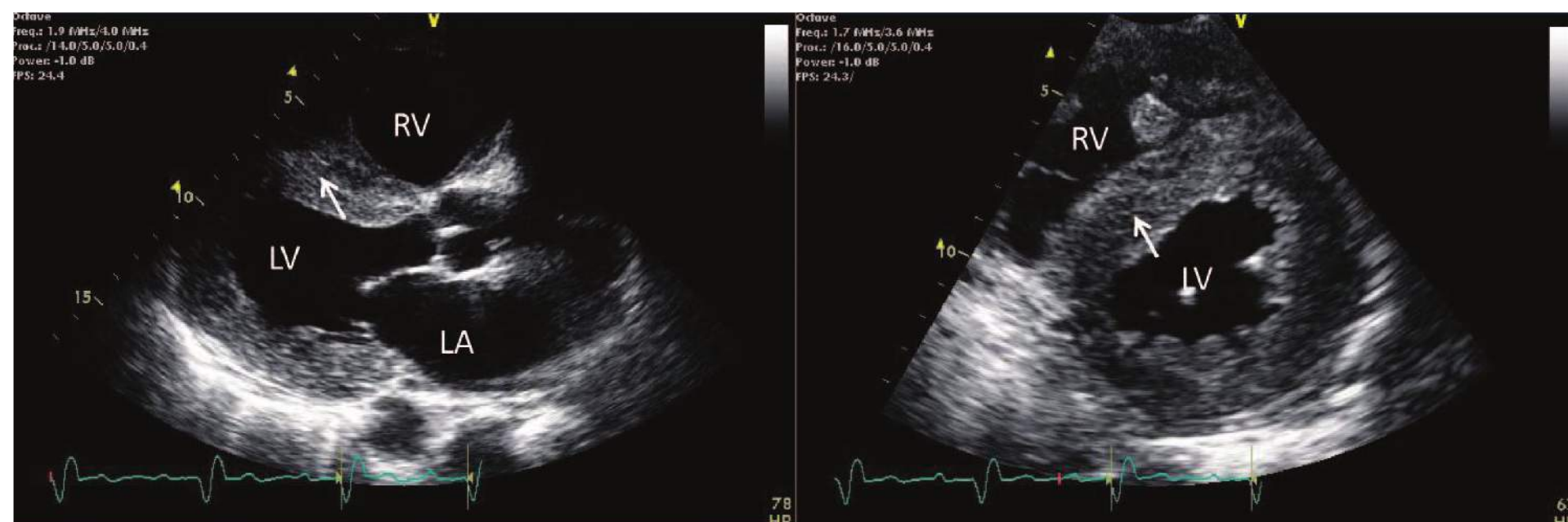


FIGURE 8 LA, left atrium; LV, left ventricle; RV, right ventricle.

21. Mrs. Jackson is a 45-year-old African American woman with a history of tobacco abuse, breast cancer (status: post mastectomy and radiation), and allergy to shellfish. She presented to your general cardiology clinic 2 weeks prior reporting dyspnea while walking up a hill near her house for the past 6 months. She has never had difficulty with this hill before. Along with the dyspnea, she experiences some vague nausea and breaks out in a sweat. Resting ECG and physical examination are both unrevealing. You referred her for an exercise single-photon emission

computed tomography (SPECT) myocardial perfusion technetium-99m (^{99m}Tc) sestamibi scan and received the results, shown in Figure 9. You quickly assess that her scan shows reversible ischemia. Which arterial territory is most likely involved in the pictured scan?

- A. Left anterior descending artery
- B. Left circumflex artery
- C. Left main coronary artery
- D. Posterior descending artery
- E. Right coronary artery

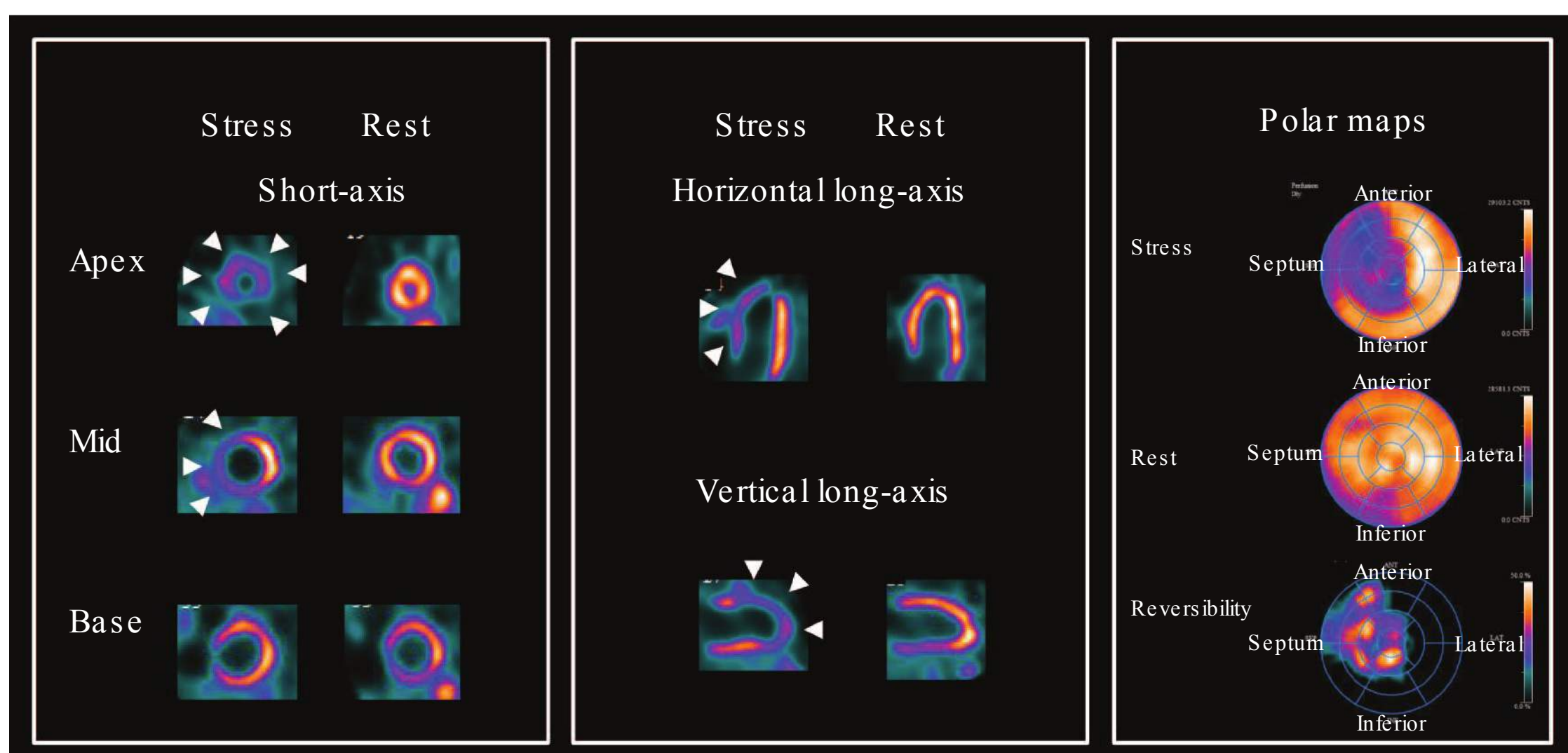


FIGURE 9

22. The SA node serves as the dominant pacemaker of the heart in normal sinus rhythm. What property of SA nodal cells allows it to act as the primary pacemaker?
- Location near the superior lateral area of the right atrium
 - More numerous intercalated discs of any other myocardial tissue
 - Most rapid phase 0 depolarization
 - Only cells with the ability to spontaneously depolarize
 - Spontaneous depolarization during phase 4 of the action potential at a more rapid rate than any other myocardial cells
23. Mr. Hendricks is a 21-year-old sommelier at a well-known restaurant in the city. His primary hobby is competitive bicycle racing, and he has a 150-km race coming up next weekend for which he has been training for the last 6 months. The race coordinators require every competitor to complete a comprehensive cardiovascular assessment prior to competing, and thus he comes to visit your clinic. On your assessment, you note a resting heart rate of 45 bpm with an occasional pause of up to 2 seconds. His blood pressure is 108/72 mmHg. He feels well and reports no syncopal or presyncopal episodes at rest or during exercise. Aside from the bradycardia, you note no other abnormalities on his examination. His ECG shows sinus rhythm with a PR interval of 128 ms, QRS duration of 80 ms, and occasional pauses as long as 2.2 seconds. Which of the following would be appropriate advice for Mr. Hendricks?
- Perform electrophysiologic evaluation for consideration of a pacemaker.
 - He should not compete in the upcoming race due to concern for bradycardia and will need a tilt-table test.
 - No further follow-up is needed. Good luck with the race!
 - Obtain a 48-hour Holter monitor tracing.
 - He should undergo a treadmill stress ECG to determine the presence of chronotropic competence.
24. A 60-year-old man is undergoing an electrophysiology study for evaluation of syncope. After careful venous cannulation and placement of conductance and pacing catheters and after administration of 0.2 mg/kg of propranolol and 0.04 mg/kg of atropine, his heart rate is 65 bpm. After stopping the drugs and allowing adequate time for wash-out, his superior/lateral right atrium is paced 140 bpm. On cessation of this overdrive pacing, his next sinus beat occurs 1800 ms later. Based on these observations, this patient can be diagnosed with which of the following?
- Amyloid cardiomyopathy
 - AV nodal disease
 - Paroxysmal atrial fibrillation
 - SA nodal disease
 - Tachy-brady syndrome
25. All of the following are reversible causes of SA node dysfunction EXCEPT:
- Hypothermia
 - Hypothyroidism
 - Increased intracranial pressure
 - Lithium toxicity
 - Radiation therapy
26. Which of the following is a risk factor for development of thromboembolism in patients with the tachycardia-bradycardia variant of sick sinus syndrome?
- Age >50 years
 - Atrial enlargement
 - Diabetes mellitus
 - Prothrombin 20210 mutation
 - None of the above; there is no increased risk of thromboembolism with the tachycardia-bradycardia variant of sick sinus syndrome
27. Normal cells within the AV node exhibit a property known as decremental conduction. If you wanted to demonstrate this property during an electrophysiology study, what maneuver could you perform?
- Pace the right atrium at serially decreasing cycle length and measure the pace-to-His conduction time.
 - Pace the ventricle and record right atrial potentials.
 - Administer atropine 0.04 mg/kg and record AV nodal conduction time by measuring the time it takes an atrial pacing beat to reach the His bundle.
 - Administer metoprolol 10 mg IV and record AV nodal conduction time by measuring the time it takes an atrial pacing beat to reach the His bundle.
 - Administer adenosine 12 mg IV and record the AV nodal recovery time.
28. An 87-year-old man with a history of well-treated hypertension and aortic stenosis has become symptomatic from his aortic stenosis over the last 2 months. Yesterday, he underwent surgical aortic valve replacement with a bioprosthetic 25-mm valve with excellent intraoperative results. He was rapidly weaned from cardiopulmonary bypass and extubated within 24 hours. Per surgical protocol, he had temporary epicardial pacing wires placed on the ventricular surface and has been pacing at 90 bpm. On rounds this morning, you briefly pause his ventricular pacing to check his underlying rhythm. You note an atrial rate of 80 bpm, but a ventricular rate of 32 bpm with a wide QRS complex. There is no relationship between the P waves and QRS complexes. This patient's ventricular bradycardia is most likely due to which of the following?
- Development of a systemic disease such as sarcoidosis or Lyme disease causing AV node dysfunction
 - Endocarditis of the new aortic bioprosthesis causing AV node block
 - SA node disease
 - Slowed AV nodal recovery after overdrive pacing
 - Surgical injury to the AV node

29. Mrs. Hellwig is a 25-year-old woman with systemic lupus erythematosus (SLE) complicated by nephropathy, hemolytic anemia, and pleuritis. Her disease is well controlled on therapy. She recently discovered that she is pregnant, and presents today for prenatal counseling. She specifically is concerned about the effect her autoimmune disease may have on the infant. You tell her that the most common cardiac complication in children born to mothers with SLE is:
- AV block
 - Coronary artery disease
 - Dilated cardiomyopathy
 - Pulmonary hypertension with right ventricular (RV) failure
 - Sterile, Libman-Sacks endocarditis
30. Mr. Hoffman, an 82-year-old former tightrope performer, presents to your office for complaints of syncope. He states that twice in the past week, he has spontaneously passed out with no warning symptoms. Once, he struck his face, and you

note that he has periorbital ecchymosis on examination. Other than this, you find nothing abnormal on examination. You request an ECG and step out of the room to begin your documentation. Shortly thereafter, your medical assistant requests your urgent presence in Mr. Hoffman's clinic room. He had another "spell" during the ECG and lost consciousness. Serendipitously, the medical assistant captured the spell on ECG, shown in Figure 10. What type of AV block is present and is matched to the appropriate treatment or diagnostic test?

- Complete SA nodal block – Permanent pacemaker implantation
- First-degree AV block – Administer atropine
- Second-degree Mobitz type II SA nodal block – Exercise treadmill study
- Second-degree Mobitz type I AV block – No intervention necessary
- Second-degree Mobitz type II AV node block – Permanent pacemaker implantation

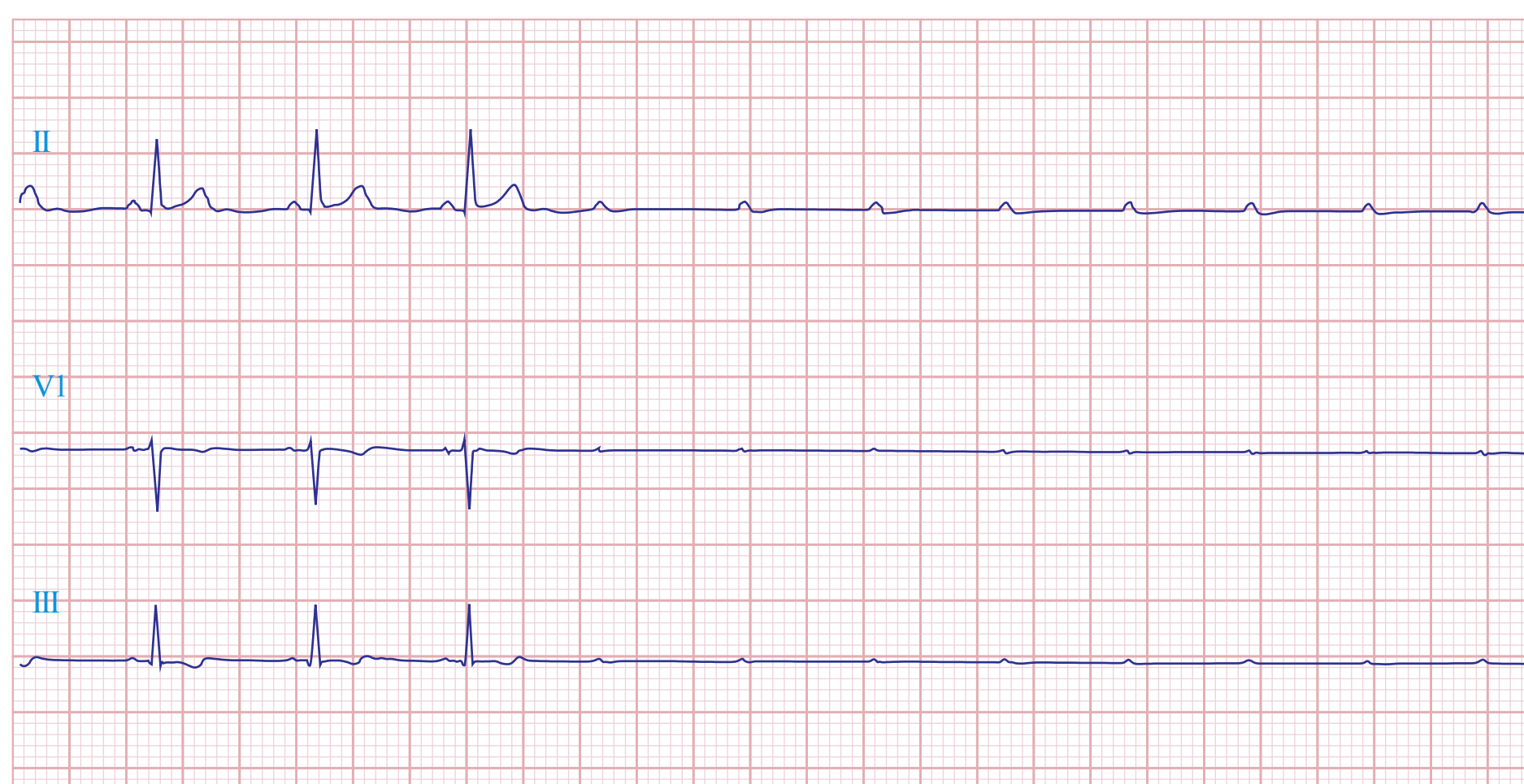


FIGURE 10

31. A 19-year-old long-distance runner, who finished in the top 10 of the local marathon last year, presents for cardiac evaluation after his primary care physician ordered a Holter monitor for screening purposes. On his Holter report, several episodes of second-degree, Mobitz I (Wenckebach) AV block were noted, all occurring during sleep. The patient reports no symptoms but thinks he may have a grandfather who had a pacemaker implanted at an advanced age. What is the most appropriate next step?
- Exercise treadmill stress ECG
 - Invasive electrophysiology study
 - Reassurance
 - Refer for pacemaker implantation
 - Serologic testing including thyroid-stimulating hormone levels
32. A 47-year-old woman with a history of tobacco abuse and ulcerative colitis is evaluated for intermittent palpitations. She reports that for the last 6 months, every 2–4 days she notes a sensation of her heart “flip-flopping” in her chest for approximately 5 minutes. She has not noted any precipitating factors and has not felt light headed or had chest pains with these episodes. Her physical examination is normal. A resting ECG reveals sinus rhythm and no abnormalities. Aside from checking serum electrolytes, which of the following is the most appropriate testing?
- Abdominal computed tomography (CT) with oral and intravenous (IV) contrast
 - Event monitor
 - Holter monitor
 - Reassurance with no further testing needed
 - Referral for electrophysiology study

33. After further testing, the patient in Question 32 is found to have several episodes of atrial premature contractions. Which of the following statements regarding the dysrhythmia in this patient is true?

- A. Atrial premature contractions are less common than ventricular premature contractions on extended ECG monitoring.
- B. Echocardiography is indicated to determine if structural heart disease is present.
- C. Metoprolol should be initiated for symptom control.
- D. The patient should be reassured that this is not a dangerous condition and does not require further evaluation.
- E. The patient should undergo stress test to determine if ischemia is present.

34. Ms. Milsap is an 18-year-old high school volleyball star with a sports scholarship to the local university. As part of her admission process, she is required to undergo a full medical assessment prior to taking part in collegiate sports. Physical examination reveals no abnormalities, although she reports the rare episode of palpitations and light-headedness. ECG reveals a PR interval of 0.06 ms, QRS duration of 140 ms, and a slurred upstroke or delta wave in the initial part of the QRS. You correctly diagnose this as Wolff-Parkinson-White pattern. Which of the following findings is reassuring that Ms. Milsap will suffer no ill effects or need catheter ablation due to this abnormality?

- A. Ability to increase the heart rate to 185 bpm on an exercise treadmill test
- B. Electrophysiology study demonstrating that the accessory pathway has both antegrade and retrograde conduction properties
- C. Electrophysiology study demonstrating that the accessory pathway is located in the posteroseptal region
- D. Exercise treadmill study demonstrating disappearance of the delta wave and wide QRS at a heart rate of 120 bpm
- E. Holter monitoring demonstrating occasional runs of atrial fibrillation

35. An 85-year-old woman with no prior cardiac history presents to the emergency department with 2 hours of palpitations. Blood pressure, oxygen saturation, and heart rate are normal, although you note an irregularly irregular rhythm on examination. ECG shows an irregularly irregular, narrow QRS without discernable P waves at a rate of 75 bpm. Echocardiogram reveals no structural heart disease. Despite the normal heart rate, the patient is quite symptomatic with her atrial fibrillation and wants to pursue achievement of sinus rhythm. All of the following interventions may be beneficial EXCEPT:

- A. Adenosine intravenously
- B. Amiodarone intravenously
- C. Direct current cardioversion
- D. Dofetilide orally
- E. Flecainide orally

36. A 79-year-old man with a history of coronary artery disease, ischemic cardiomyopathy with a last left ventricular (LV) ejection fraction of 30%, and hypertension presents to your office with no new complaints. Blood pressure is 108/56 mmHg, heart rate is 88 bpm, and arterial oxygen saturation is 98%. His rhythm strip is shown in Figure 11. Based on this ECG, the patient now has a definite (class I) indication for which of the following therapies?



FIGURE 11

- A. Amiodarone 400 mg daily
- B. Aspirin 325 mg daily
- C. Flecainide 600 mg PRN palpitations
- D. Systemic anticoagulation with warfarin or a novel oral anticoagulant
- E. Transesophageal echocardiography followed by direct current (DC) cardioversion

37. A 43-year-old woman is seen in the emergency department after sudden onset of palpitations 30 minutes prior to her visit. She was seated at her work computer when the symptoms began. Aside from low back pain, she is otherwise healthy. In triage, her heart rate is 178 bpm and blood pressure is 98/56 mmHg with normal oxygen saturation. On physical examination, she has a “frog sign” in her neck and tachycardia but is otherwise normal. ECG shows a narrow complex tachycardia without identifiable P waves. Which of the following is the most appropriate first step to manage her tachycardia?

- A. 5 mg metoprolol IV
- B. 6 mg adenosine IV
- C. 10 mg verapamil IV
- D. Carotid sinus massage
- E. DC cardioversion using 100 J

38. Which of the following statements regarding restoration of sinus rhythm after atrial fibrillation is true?

- A. Dofetilide may be safely started as an outpatient.
- B. In patients who are treated with pharmacotherapy and are found to be in sinus rhythm, a prolonged Holter monitor should be worn to determine if anticoagulation can be safely stopped.
- C. Patients who have pharmacologically maintained sinus rhythm after atrial fibrillation have improved survival compared with patients who are treated with rate control and anticoagulation.
- D. Recurrence of atrial fibrillation is uncommon when pharmacotherapy is used to maintain sinus rhythm.

39. A 76-year-old woman with a history of hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and osteoporosis presents to the emergency department after a fall at home followed immediately by intense left hip pain. She was found by a neighbor after several hours. The patient cannot remember if she lost consciousness. She is exquisitely tender to palpation over the left hip, and her leg is shortened and externally rotated. Her mucous membranes are dry, and her skin tents

easily. Blood pressure is 170/80 mmHg and heart rate is 130 bpm. Her rhythm strip is shown in Figure 12. What is the most appropriate first step for her tachycardia?

- Adenosine 6 mg IV
- DC cardioversion
- Digoxin 250 μ g IV
- Metoprolol 5 mg IV
- Pain control and IV hydration

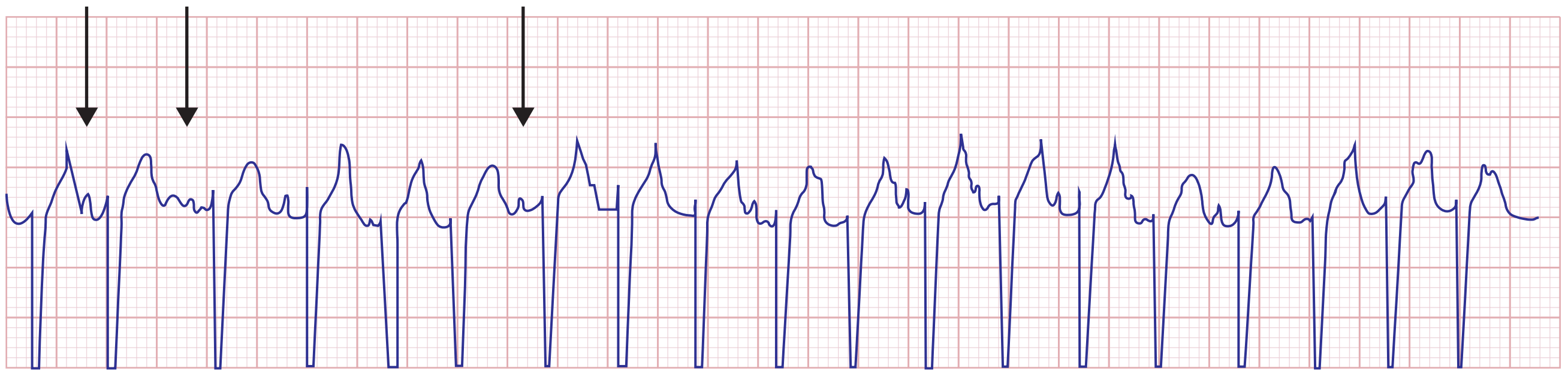


FIGURE 12

40. A young woman is brought to the emergency department after witnesses observed her suddenly lose consciousness while jogging in the nearby park. She has a fractured nose and broken teeth from her fall. She does not have identification. She is nonresponsive to painful stimuli. Blood pressure is 50/palp and heart rate is close to 280 bpm. A 12-lead ECG is shown in Figure 13. What is the next most appropriate step?

- Amiodarone 150 mg IV stat
- Lidocaine 1 mg IV stat
- Metoprolol 10 mg IV
- DC defibrillation
- Emergent CT scan with contrast to evaluate for pulmonary embolism

41. What is the underlying rhythm in the patient in Question 40?

- Atrial fibrillation with antegrade conduction through an accessory tract
- Atrial flutter with 1:1 conduction
- AV reentry tachycardia
- AV nodal reentry tachycardia
- Ventricular tachycardia

42. A 67-year-old man with a history of hypertension and hyperlipidemia presented 3 hours ago to the emergency department with crushing substernal chest pain and dyspnea of acute onset. There, ST elevations were

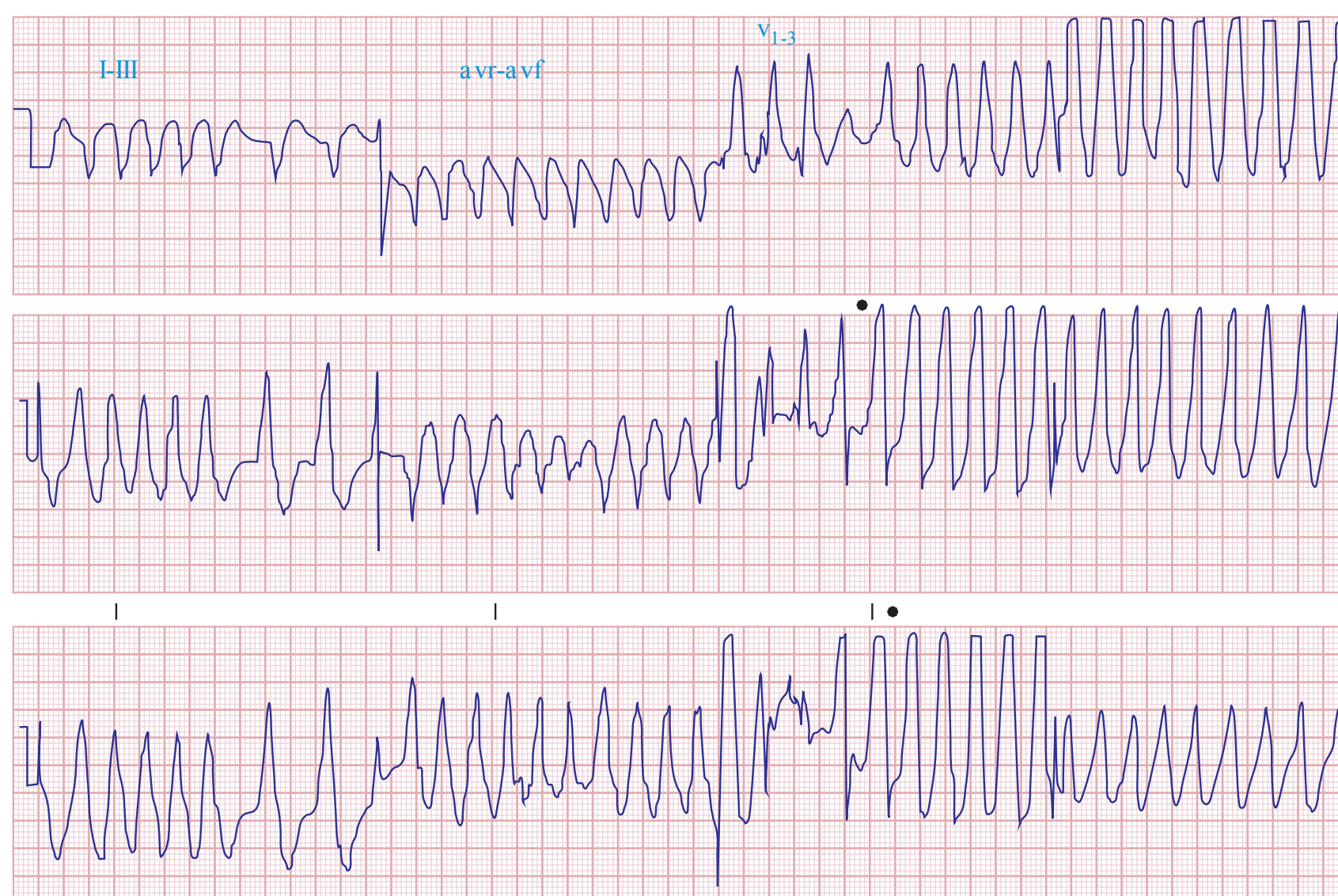


FIGURE 13

noted in the anterior and lateral leads on his ECG, and thrombolytics were administered. He was admitted to the cardiac intensive care unit. Now, his nurse calls you to his room because he is having unusual tracings on his monitor. A sample rhythm strip recorded from lead V_6 is shown in Figure 14. What rhythm does this represent?

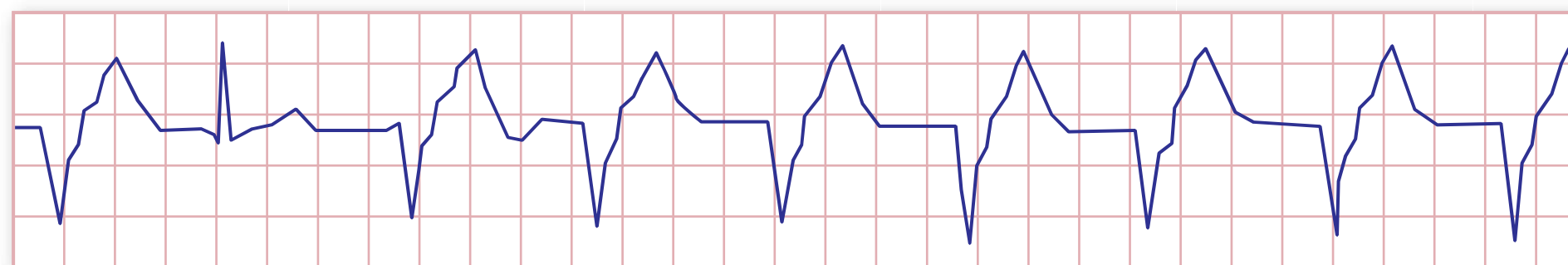


FIGURE 14

- A. Atrial fibrillation
- B. Complete heart block with a junctional escape
- C. Idioventricular rhythm
- D. Normal sinus rhythm with a left bundle branch block
- E. Ventricular tachycardia

43. You are having a quiet shift in the local emergency department. For the past 4 days, there has been a large snowstorm limiting traffic, and people have generally stayed indoors and out of harm's way. Suddenly, the emergency medical personnel arrive with a middle-aged woman who is obtunded. Her downstairs neighbors noted that they had not seen her for the past 4 days (since the snow started) and alerted the police who found her unconscious on her floor. On your assessment, you can barely feel a radial pulse. You note a dialysis fistula graft in her left arm. Blood pressure is 60/palp, and her ECG tracing is shown in Figure 15. You rapidly set up for defibrillation and request a full chemistry panel. What electrolyte abnormality do you expect to find?

- A. Hypercalcemia
- B. Hyperkalemia
- C. Hypokalemia
- D. Hypomagnesemia
- E. Hypophosphatemia

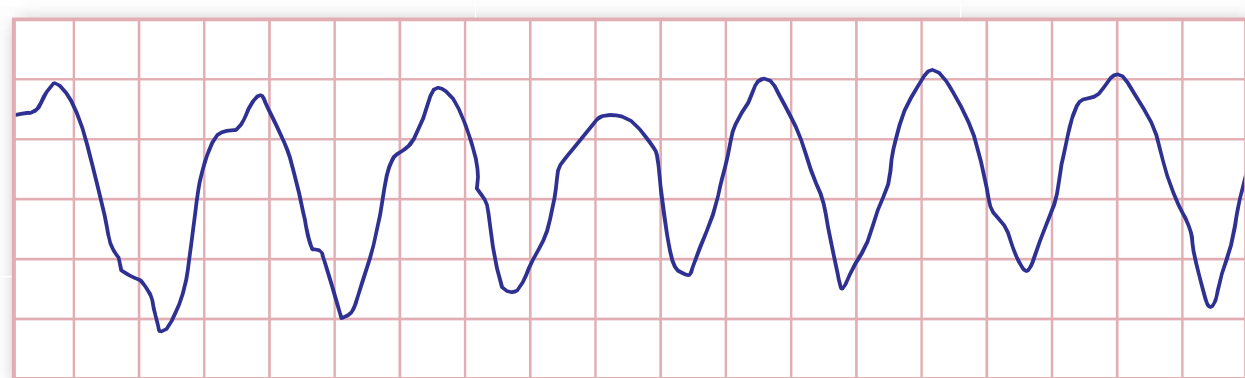


FIGURE 15

44. A 71-year-old woman with ischemic cardiomyopathy and a left ventricular ejection fraction of 38% has been hospitalized for the past week with acute decompensated heart failure. After diuresis and medication optimization, she is feeling immensely better. She is on the maximally tolerated doses of an angiotensin-converting enzyme (ACE) inhibitor, β -blocker, and appropriate diuretic dose. You are planning for discharge today. On rounds, the nurse notes that the patient had several short (5–10 beats) runs of nonsustained ventricular tachycardia (NSVT) and multiple premature ventricular

contractions (PVCs) overnight, although she remained asymptomatic. A medical student on the team asks if the NSVT carries any prognostic significance and if any intervention is needed. What is the most appropriate response?

- A. "NSVT is common in patients with cardiomyopathy and carries no significance."
- B. "NSVT is concerning in this patient. We should suppress the PVCs and NSVT with amiodarone."
- C. "NSVT is associated with an increased mortality in patients with heart failure. We will refer her for an automated implantable defibrillator."
- D. "NSVT is associated with an increased mortality in patients with heart failure. We should suppress the NSVT with flecainide."
- E. "NSVT is associated with an increased mortality in patients with heart failure. However, suppression of PVCs and NSVT with antiarrhythmic drugs does not change this prognosis."

45. You are taking care of Mr. Wittstine in the cardiac intensive care unit. He is a 62-year-old man with hypertension, hyperlipidemia, and tobacco abuse who suffered a massive anterior myocardial infarction 4 days prior. He presented late to the emergency department, and thus despite expeditious primary coronary intervention with angioplasty and stent placement to his left anterior descending artery, echocardiogram today shows an ejection fraction of 25%. He has had no ventricular arrhythmias. He still feels slightly short of breath, and your examination reveals bilateral pulmonary rales and an elevated jugular venous pulse. Other than aspirin, clopidogrel, and atorvastatin, he is on no other therapy. All of the following therapies will reduce his mortality over the next 40 days EXCEPT:

- A. Automated implantable defibrillator
- B. Eplerenone
- C. Lisinopril
- D. Metoprolol
- E. All of the above will reduce Mr. Wittstine's mortality

46. A 21-year-old college student who is studying musical education at the local university recently joined a chorus group. However, whenever she stands to sing a solo, she notes the onset of palpitations and light-headedness. While she has never lost consciousness, she occasionally has to sit down due to the dizziness. She presents to your clinic for evaluation. Her physical examination is completely normal, as is her baseline resting ECG. You ask her to sing a solo for the clinic staff and simultaneously record a 12-lead ECG (seen in Figure 16). Her singing voice is

lovely, but she quickly experiences the symptoms and has to stop. You refer her for echocardiography and cardiac MRI, which are normal. You suspect that the patient's palpitations are due to which of the following?

- A. Arrhythmogenic right ventricular dysplasia
- B. Brugada syndrome
- C. Hypertrophic cardiomyopathy
- D. Left ventricular intraventricular tachycardia
- E. Right ventricular outflow tract ventricular tachycardia

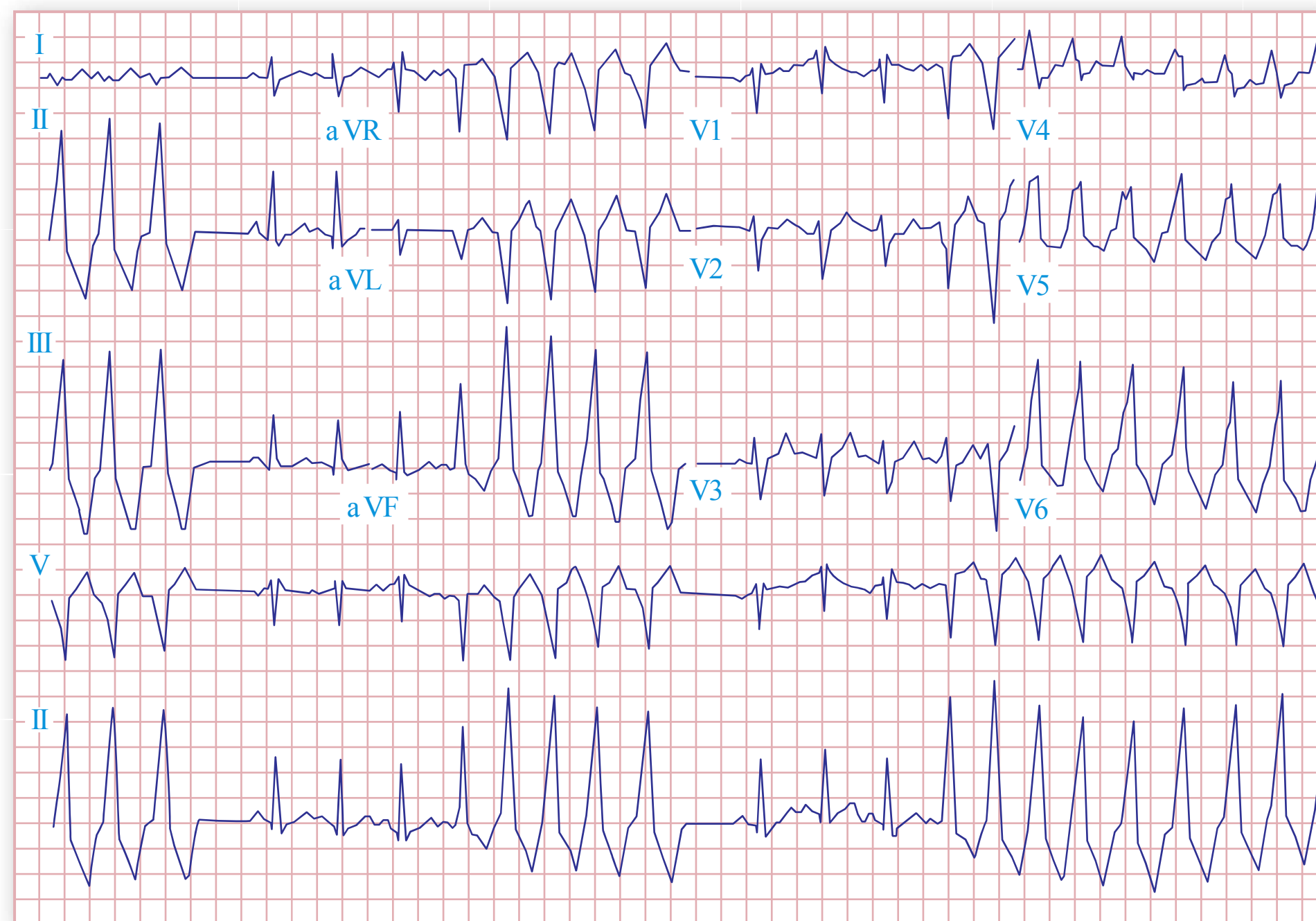


FIGURE 16

47. A 47-year-old woman who is maintained on methadone for a prior history of narcotic abuse recently contracted an upper respiratory tract infection, and her friend offered her some leftover erythromycin pills. Today, she felt multiple episodes of palpitations and light-headedness, prompting presentation to the emergency department. There, rhythm strip demonstrated multiple nonsustained runs of the arrhythmia featured in Figure 17. You administer 2 mg of IV magnesium sulfate; however, the episodes of nonsustained arrhythmia do

not abate. Her laboratory examination shows a normal potassium level. What is the next most appropriate step?

- A. Metoprolol 5 mg IV repeatedly until her resting heart rate is 60 bpm
- B. Amiodarone 150 mg IV
- C. Emergent referral for implantable defibrillator
- D. IV isoproterenol infusion titrated to a rate of 100–120 bpm
- E. Sedation and defibrillation

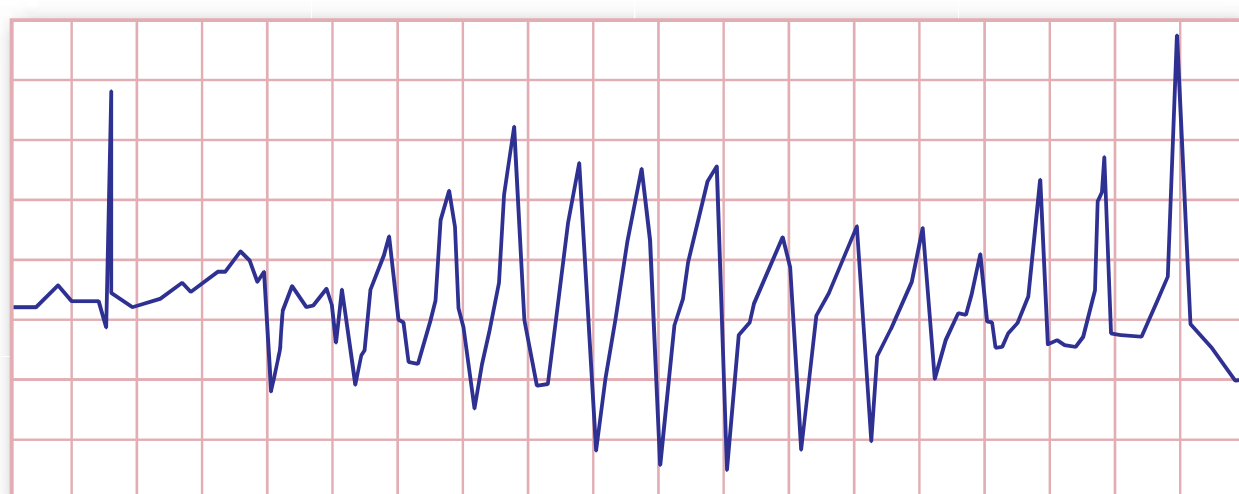


FIGURE 17

48. In an ECG with wide complex tachycardia, which of the following clues most strongly supports the diagnosis of ventricular tachycardia?

- A. Atrial-ventricular dissociation
- B. Classic right bundle branch block pattern
- C. Irregularly irregular rhythm with changing QRS complexes
- D. QRS duration >120 ms
- E. Slowing of rate with carotid sinus massage

49. An 18-year-old man with no prior past medical history presents for his required medical assessment before beginning his freshman year at the local university. His history and examination uncover no concerning symptoms or signs. However, his ECG shows an irregular rhythm and is shown in Figure 18. What is the most appropriate next step?

- A. Echocardiography
- B. Electrophysiology study and planned ablation of an ectopic atrial focus
- C. Exercise ECG stress test
- D. Holter monitor to define arrhythmia burden
- E. Reassurance

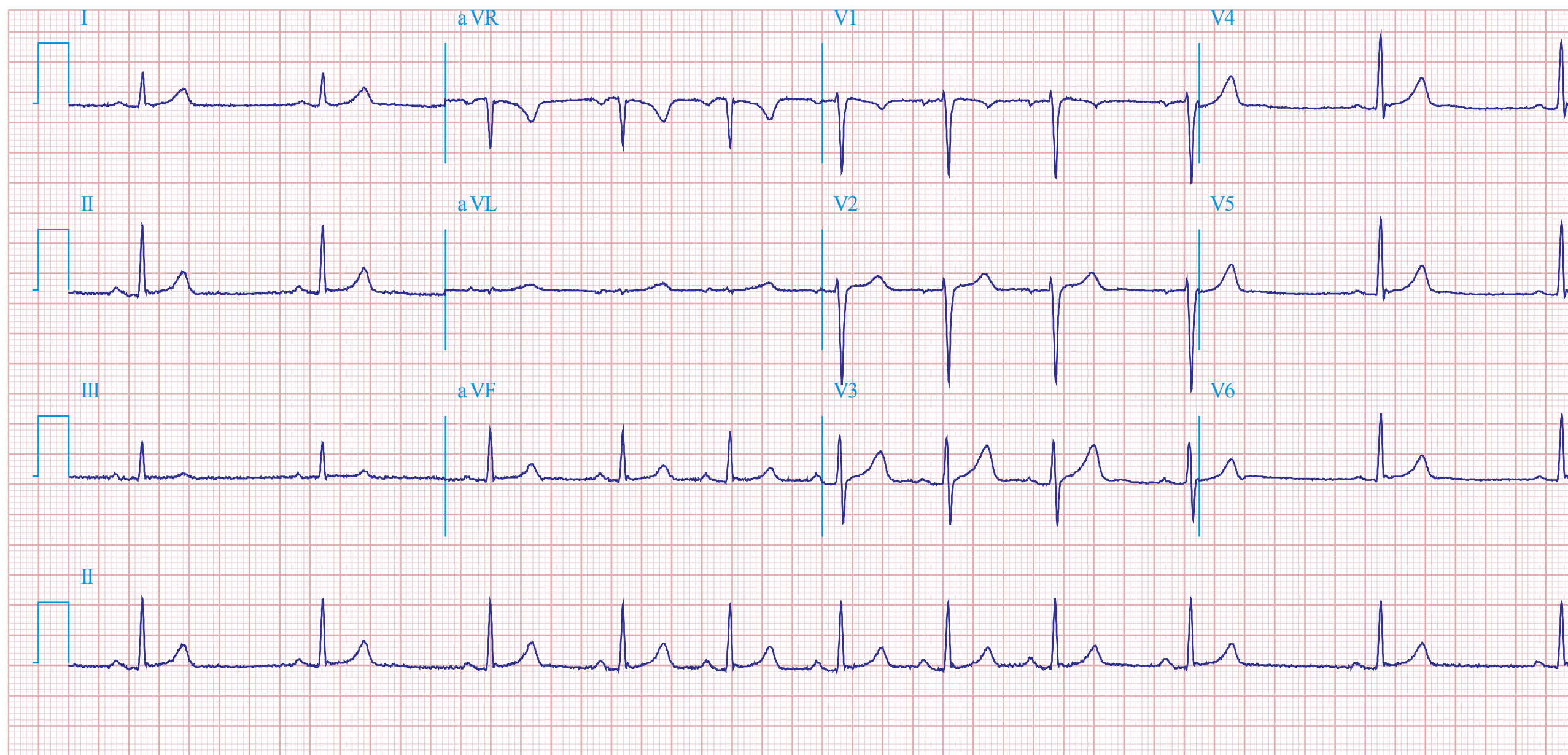


FIGURE 18

50. Ms. Hardy is a 22-year-old triathlete with a history of type 1 diabetes mellitus. Unfortunately, her pharmacy provided her with an expired batch of insulin due to a clerical error, and she presented to the hospital in diabetic ketoacidotic crisis 3 days ago. With aggressive

hydration, electrolyte repletion, and insulin administration, her ketoacidotic crisis was reversed. She is feeling much better and is planned for discharge tomorrow. You are called by the monitor station and told that Ms. Hardy is bradycardic. Her ECG is shown in Figure 19. You check on her and note

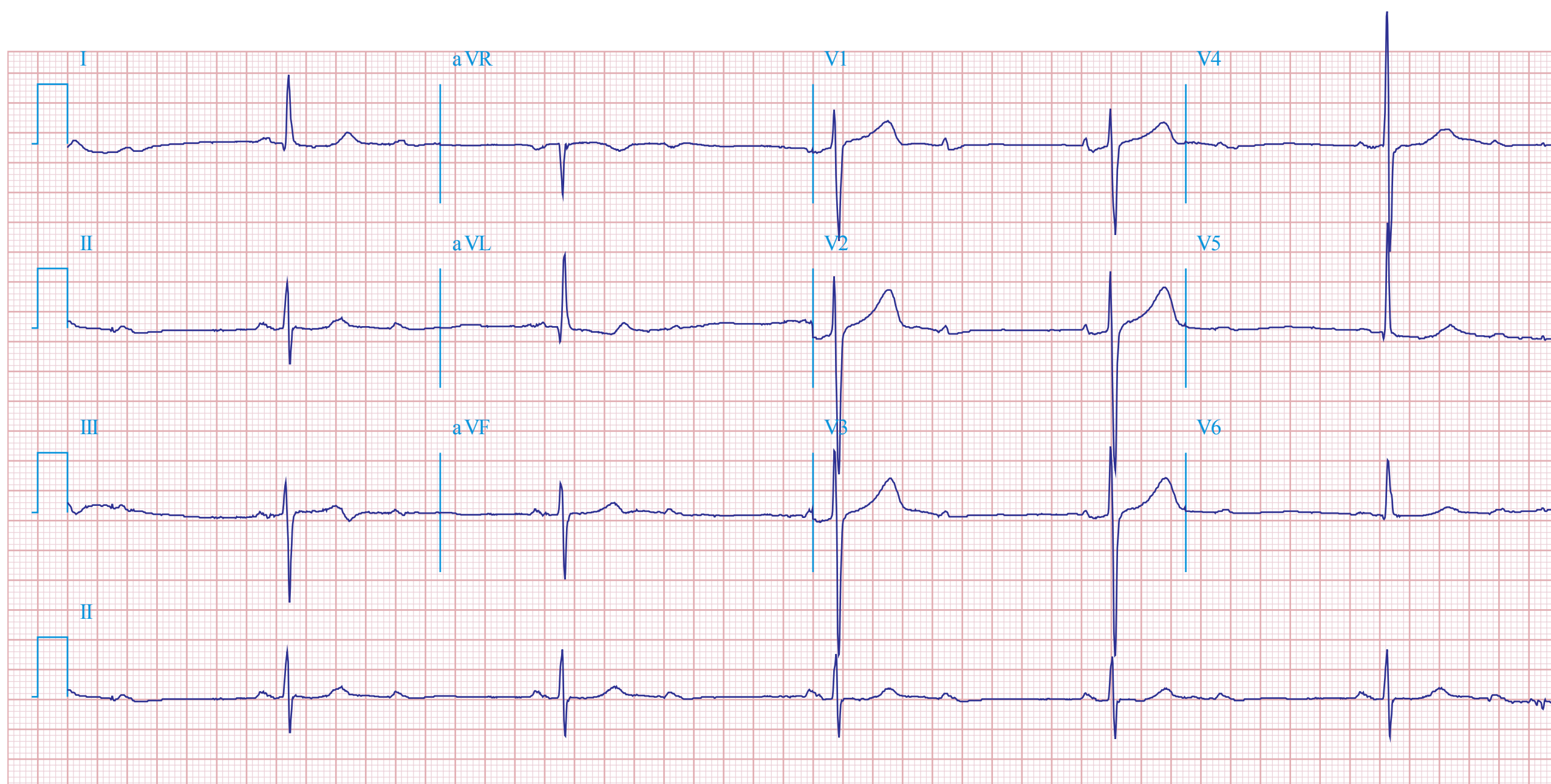


FIGURE 19

that she is sleeping soundly. The anatomic location of her heart block is likely where?

- A. AV node
 - B. Bachmann bundle
 - C. His bundle
 - D. Left bundle branch
 - E. SA node
- 51.** If you were to administer atropine intravenously to Ms. Hardy, the patient in Question 50, you would expect which of the following to occur?
- A. Increase sinus rate and maintain 2:1 AV block
 - B. Increase sinus rate and improve heart block to 1:1 conduction
 - C. Increase sinus rate and worsen heart block to >2:1
 - D. No change in sinus rate and worsen heart block to >2:1
 - E. No change

52. An 87-year-old man with Parkinson disease takes levodopa. After running out of his medication and failing to obtain a refill, he presents to the emergency department with a parkinsonian exacerbation. On initial evaluation, he has the ECG shown in Figure 20. Which of the following is the next most appropriate step?

- A. Anticoagulation with IV heparin
- B. Check serum thyroid-stimulating hormone (TSH) and obtain targeted respiratory history
- C. DC cardioversion
- D. Metoprolol 5 mg IV
- E. No further testing or intervention

53. Mr. Tillman is a 68-year-old man with a history of nonischemic cardiomyopathy, hypertension, and a transient ischemic attack 6 months ago with no obvious cause after appropriate workup. He presents to the emergency department with 5 days of not feeling

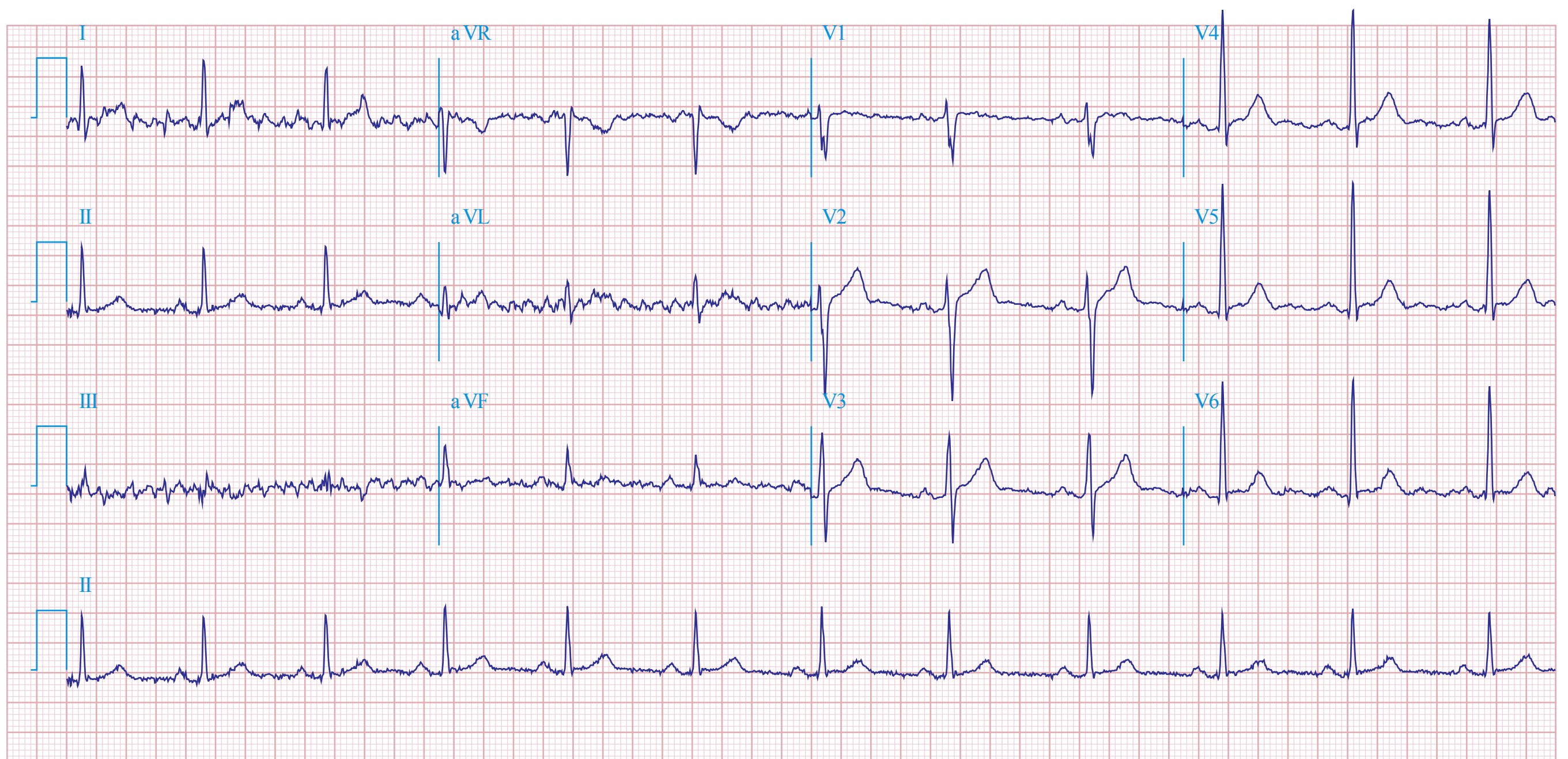


FIGURE 20

well. On examination, he appears tired. Blood pressure is 110/78 mmHg, and his heart rate is 150 bpm. His jugular veins are not distended and lungs are clear. His ECG is shown in Figure 21. You appropriately administer 5 mg of IV metoprolol twice, which brings his heart rate down to 75 bpm. He feels much better. You consult the cardiac electrophysiologist for consideration of ablation of the etiologic arrhythmia. What is the next most appropriate step?

- A. Amiodarone
- B. Aspirin
- C. Digoxin
- D. Furosemide
- E. Systemic anticoagulation

54. Ms. Schoop is a 22-year-old pottery store owner who presents to you for evaluation of palpitations. Her ECG is shown in Figure 22. She likely has a bypass accessory tract located in the:

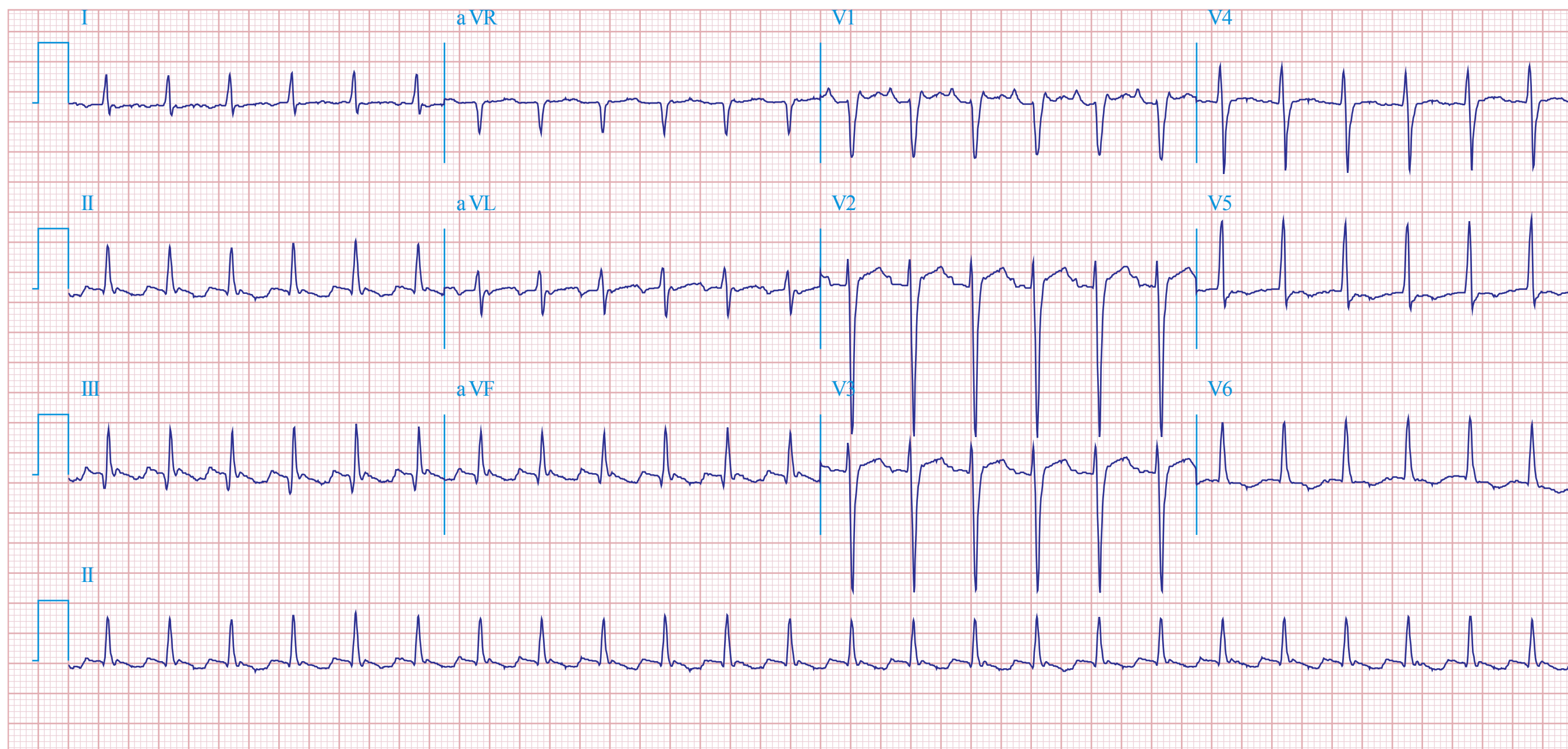


FIGURE 21

- A. Anterior septum
- B. Anterolateral left ventricle
- C. Inferior left ventricle
- D. Inferior septum
- E. Right ventricle

55. A 68-year-old man with a history of myocardial infarction and congestive heart failure is comfortable at rest. However, when walking to his car, he develops dyspnea, fatigue,

and sometimes palpitations. He must rest for several minutes before these symptoms resolve. Which of the following is his New York Heart Association classification?

- A. Class I
- B. Class II
- C. Class III
- D. Class IV

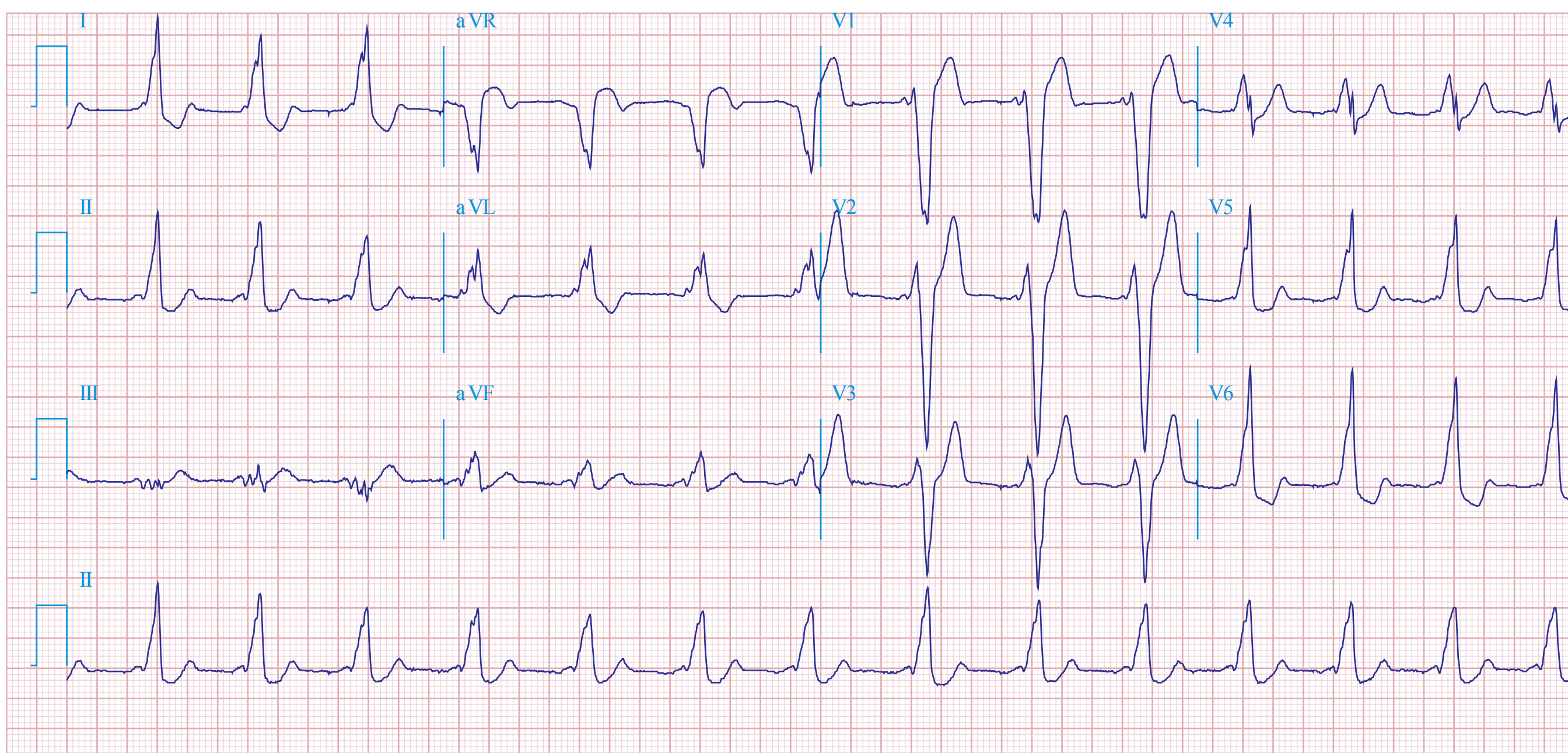


FIGURE 22

- 56.** A 47-year-old postmenopausal woman is seen for onset of severe dyspnea over the last few weeks. She reports no preceding chest pain, cough, sputum, or fever, although she does report leg swelling. Physical examination is notable for a blood pressure of 145/78 mmHg and heart rate of 123 bpm. Exophthalmos is present, as well as bilateral inspiratory crackles occupying approximately one-third of the lower chest with neck vein distention. She has a third heart sound with no murmur. Bilateral lower extremity edema is also present with warm extremities and a fine hand tremor. Which of the following is the most likely pathophysiologic explanation for her heart failure?
- Anemia with high-output state
 - Chronic systemic hypertension with resultant left ventricular hypertrophy and nonsystolic heart failure
 - Hemochromatosis with subsequent restrictive cardiomyopathy
 - Myocardial infarction with depressed left ventricular systolic function
 - Tyrosinosis with high-output state
- 57.** Regarding the epidemiology and prognosis of heart failure, which of the following statements is true?
- Among patients with heart failure with reduced ejection fraction, coronary artery disease is the most common cause.
 - Anemia is a frequent cause of heart failure among patients with a previously structurally normal heart.
 - Due to advances in medical and device therapy, the prognosis of all patients with heart failure is now excellent, with >90% surviving more than 1 year after diagnosis.
 - Familial, or genetic, cardiomyopathy is quite rare, although it should be screened for aggressively to aid diagnosis and early treatment among presymptomatic affected family members.
 - Heart failure with preserved ejection fraction makes up a minority of the total population of patients with heart failure.
- 58.** From a pathophysiologic perspective, all of the following are upregulated in heart failure with reduced ejection fraction EXCEPT:
- Angiotensin II
 - B-type natriuretic peptide (BNP)
 - Calcium uptake into the sarcoplasmic reticulum
 - Norepinephrine
 - Tumor necrosis factor
- 59.** All of the following clinical conditions are associated with orthopnea EXCEPT:
- Abdominal ascites
 - Abdominal obesity
 - Diaphragmatic weakness
 - Heart failure
 - Hepatopulmonary syndrome
- 60.** A 67-year-old man presents to the emergency department with shortness of breath. He is found to have an elevated serum BNP. In addition to heart failure, all of the following may also cause an elevation in BNP EXCEPT:
- Advanced age
 - Female sex
 - Obesity
 - Pulmonary embolism with right heart strain
 - Renal insufficiency
- 61.** You are taking care of a patient with cor pulmonale in the medical intensive care unit. Unfortunately, he suffered a respiratory arrest at home and requires intubation and mechanical ventilation. Currently, with a tidal volume of 500 mL, FiO₂ of 0.4, positive end-expiratory pressure of 20 mmHg, and respiratory rate of 20, his pH is 7.40, PCO₂ is 40 mmHg, and oxygen saturation is 86%. You are concerned about the afterload experienced by his right ventricle. All of the following are likely to increase his right ventricular afterload EXCEPT:
- Increasing FiO₂ to increase arterial oxygen saturation to 95%
 - Increasing positive end expiratory pressure (PEEP) to 35 mmHg
 - Increasing tidal volume to 750 mL
 - Reducing respiratory rate to 10
- 62.** Mr. George is a 52-year-old man with longstanding hypertension and poorly controlled diabetes. He presents complaining of several months of breathlessness with exertion, acute episodes of shortness of breath when recumbent, and lower extremity edema. On examination, he has an elevated jugular venous pulse and an S₄ on auscultation. Echocardiography shows a left ventricular ejection fraction of 55% with a large left atrium. You suspect this patient has the syndrome of heart failure with preserved ejection fraction (HFpEF). Drugs targeting which of the following have convincingly demonstrated mortality reduction for patients with HFpEF?
- Angiotensin-converting enzyme
 - Angiotensin receptor
 - Phosphodiesterase-5
 - Sodium-potassium-ATPase
 - None of the above
- 63.** You are evaluating a 64-year-old woman with a history of nonischemic cardiomyopathy. She presents to the emergency department for shortness of breath. You note that she has gained 11 kg since her last cardiology appointment 2 months ago. Physical examination confirms findings

associated with acute decompensated heart failure, including pulmonary rales, elevated jugular venous pulse, abdominal ascites, lower extremity edema, and a square wave blood pressure Valsalva response. Her extremities are warm, and blood pressure is 110/78 mmHg with a heart rate of 75 bpm. Her laboratory studies return with a sodium of 128 mEq/L and creatinine of 2.5 mg/dL (which is increased from her prior level of 1.2 mg/dL). Chest x-ray shows a diffuse alveolar filling pattern consistent with pulmonary edema. What is the next most appropriate step?

- A. Administer digoxin 250 µg IV
 - B. Administer furosemide 40 mg IV
 - C. Insert a large-bore central IV line and prepare for ultrafiltration
 - D. Insertion of a pulmonary artery catheter for hemodynamic monitoring
 - E. Start dobutamine at 5 µg/kg/min and titrate to a urine output of 1 mL/kg/h
- 64.** Which of the following statements regarding nesiritide is true in patients with acute decompensated heart failure requiring invasive hemodynamic monitoring?
- A. Nesiritide has no significant effect on blood pressure.
 - B. Nesiritide improves renal perfusion in states of acute decompensated heart failure.
 - C. Nesiritide is associated with a decreased rate of rehospitalization, but not death, from acute decompensated heart failure.
 - D. Nesiritide reduces pulmonary capillary wedge more rapidly than IV nitrates.
 - E. None of the statements are true.
- 65.** Mr. Jones is a 21-year-old man who presents to the emergency department with several days of worsening shortness of breath and lethargy 1 week after a viral upper respiratory tract infection. His family brought him in after he lacked the energy to rise from the couch unassisted. His blood pressure is 88/72 mmHg, heart rate is 115 bpm, and room air oxygen saturation is 90%. Physical examination reveals pulmonary crackles, elevated jugular venous pressure, an audible S₃ gallop, and cool extremities. He is lethargic and slow to respond to questions. Laboratory analysis reveals a creatinine of 2.3 mg/dL, elevated BNP level, and mildly elevated lactate. Bedside echocardiography reveals a left ventricular ejection fraction of 15% with global hypokinesis. You start dobutamine at 5 µg/kg/min and prepare to insert a pulmonary artery catheter for hemodynamic monitoring. Which of the following hemodynamic parameters is most likely increased?
- A. Cardiac output
 - B. Left ventricular stroke work index
 - C. Mixed venous oxygen saturation
 - D. Stroke volume
 - E. Systemic vascular resistance
- 66.** Which of the following medications has been shown to reduce mortality in heart failure with reduced ejection fraction?
- A. Bucindolol
 - B. Nebivolol
 - C. Metoprolol succinate
 - D. Metoprolol tartrate
 - E. All of the above
- 67.** You are seeing a patient with newly diagnosed nonischemic cardiomyopathy with a left ventricular ejection fraction of 35%. He is euvolemic and New York Heart Association (NYHA) class I in terms of symptoms severity. His blood pressure is 120/78 mmHg and heart rate is 80 bpm. You know that, eventually, you would like him on optimal doses of a β-blocker and an ACE inhibitor. Which of the following represents the appropriate order of initiation and dose titration of these medications?
- A. Coinitiate ACE inhibitor and β-blocker at low dose. Titrate each up every 2–4 weeks to highest tolerated dose.
 - B. Initiate ACE inhibitor and titrate to highest tolerated dose. Then initiate β-blocker and titrate to highest tolerated dose.
 - C. Initiate ACE inhibitor at low dose. Then initiate β-blocker at low dose. Alternate titrating the dose up for each drug to the highest tolerated dose for both.
 - D. Initiate β-blocker and titrate to highest tolerated dose. Then initiate ACE inhibitor and titrate to highest tolerated dose.
 - E. The specific strategy does not matter so much as the goal of initiating both ACE inhibitor and β-blocker in a timely manner and titrating both to their optimal, highest tolerated doses.
- 68.** You are seeing a 72-year-old woman with a history of ischemic cardiomyopathy and left ventricular ejection fraction of 35%. She is NYHA class II in terms of symptoms. She is on lisinopril 40 mg daily, carvedilol 25 mg twice daily, and spironolactone 25 mg daily. Her blood pressure is 102/82 mmHg and heart rate is 60 bpm. Which of the following additional medications will further reduce her mortality?
- A. Aliskiren
 - B. Digoxin
 - C. Ivabradine
 - D. Valsartan
 - E. None of the above
- 69.** You are following a 57-year-old man who suffered a large anterior myocardial infarction 8 months ago. Despite a late presentation to medical care (>5 hours after chest pain onset), he underwent primary coronary intervention with excellent angiographic result. After that stay in the hospital, he has been followed by you regularly and maintains excellent medication compliance. Today, his heart rate is

65 bpm and blood pressure is 104/82 mmHg. He looks quite well and reports absolutely no symptoms, even during a recent elk hunting trip requiring long days of hiking up and down hills. His medications are aspirin, clopidogrel, atorvastatin, carvedilol, and valsartan. His ECG shows sinus rhythm with a right bundle branch block and QRS duration of 135 ms. Echocardiography today shows an ejection fraction of 25% with a large area of anterior dyskinesis consistent with aneurysm. Which of the following therapies is indicated to reduce this patient's mortality?

- A. Implantable cardioverter defibrillator
- B. Implantable cardioverter defibrillator with cardiac resynchronization capability (coronary sinus lead)
- C. Ivabradine
- D. Surgical ventricular remodeling
- E. None of the above

70. You are evaluating a 25-year-old man with a history of nonischemic cardiomyopathy who underwent an orthotopic heart transplant 18 months ago. He has done very well with his course and comes today for a routine visit. You note that his blood pressure is 128/82 mmHg and heart rate is 90 bpm. His ECG appears typical for sinus rhythm with a normal PR interval and P-wave axis. On review of his chart, you note that his resting heart rate has been almost exactly 90 bpm on every visit. He feels fine. Which of the following is the most appropriate next step for his elevated resting heart rate?

- A. Exercise treadmill ECG testing to evaluate for chronotropic competence
- B. Initiate diltiazem 120 mg twice daily
- C. Initiate metoprolol tartrate 25 mg twice daily
- D. Reassurance
- E. Refer for electrophysiology study to evaluate for ectopic atrial tachycardia

71. You are appointed to an advisory position with the government's committee on organ transplantation. The committee chairman is curious about enacting a nationwide organ-sharing strategy for heart transplant, wherein only position on the transplant list and wait time would determine organ allocation order (instead of any geographic concerns). You advise the committee chairman that this strategy is not beneficial because:

- A. Blood types are grouped nonrandomly nationally, precluding true nationwide sharing
- B. The different regions have highly variable criteria for severity of illness determination
- C. The financial structure of reimbursement/payment nationwide would not allow it
- D. There is a physiologic limit on "cold ischemic" (time out of body) time for harvested hearts that would preclude nationwide sharing.
- E. None of the above is true

72. A 28-year-old man presents to the emergency department for dyspnea on exertion. He had an orthotopic heart transplant for nonischemic cardiomyopathy 5 years ago and, in general, has done quite well except for one cytomegalovirus reactivation within the first year. He reports that for the past 3 months, he has noticed that with decreasing amounts of exertion he has been having limiting dyspnea. He is adamant that he is experiencing no chest pain or pressure during these episodes. He has been perfectly compliant with his regimen of tacrolimus, mycophenolate mofetil, and low-dose prednisone. Echocardiography reveals a normal LV function with normal LV wall thickness. His resting ECG shows normal sinus rhythm at a rate of 80 bpm. Which of the following is the most likely cause of his symptoms?

- A. Antibody-mediated rejection
- B. Cellular rejection
- C. Coronary artery disease
- D. Endocarditis
- E. Medication side effect

73. You are seeing Mrs. Block in the heart failure clinic. She is a 68-year-old woman with a past history of diffuse large B-cell lymphoma treated successfully with chemotherapy and eventual bone marrow transplantation 15 years previously. Unfortunately, she suffered chemotherapy-related cardiomyopathy and now has an ejection fraction of 15%. She has been hospitalized four times in the last 6 months with acute decompensated heart failure. She is currently NYHA class III to IV regarding symptoms. Recently, she underwent a cardiopulmonary exercise stress test documenting a peak oxygen consumption of 9 mL/kg/min. She is on optimal medical therapy. At a multidisciplinary transplantation meeting, she was deemed to not be a candidate for orthotopic heart transplantation due to her age and prior malignancy. She asks what other options are available for her, as her number one priority is to live 3 more years to see her grandson graduate high school. Which of the following is an appropriate response?

- A. "Continuous infusion of milrinone will improve cardiac function and survival."
- B. "A left ventricular assist device can improve quality of life but provides no survival benefit over optimal medical care."
- C. "A left ventricular assist device can improve survival over the initial 2–5 years more than optimal medical therapy."
- D. "Stem cell implantation has been shown to prolong life in patients with end-stage cardiomyopathy."
- E. "There are no other options for prolonging life, and we should consider palliative measures in the future."

74. Which of the following statements regarding the epidemiology of congenital heart disease (CHD) in the United States is true?

- A. CHD remains extremely rare, complicating 0.1% of all live births.
- B. Given advances in surgical techniques and pre- and postnatal care, survival for a neonate with CHD now approaches 90%.
- C. Given the declining rates of pregnancy in women with CHD, the incidence of CHD in neonates is declining.
- D. The population of adults with CHD is declining given improved prenatal screening efforts.
- E. Women with CHD are at no increased risk for complications during pregnancy compared with the normal population.
- 75.** A 62-year-old man is being evaluated for mitral valve replacement surgery for severe mitral regurgitation. As part of his evaluation, he undergoes a transesophageal echocardiogram that demonstrates a small jet of right-to-left Doppler flow during systole across the atrial septum. The jet is located roughly in the middle of the septum and occurs when a small flap of tissue swings open <1 mm. There is no diastolic flow nor is there a visible opening in any part of the septum during diastole. Which of the following explains the finding on echocardiography?
- A. Ostium primum atrial septal defect
- B. Ostium secundum atrial septal defect
- C. Partial anomalous pulmonary venous return
- D. Patent foramen ovale
- E. Sinus venosus atrial septal defect
- 76.** You are evaluating a 21-year-old man in clinic. He occasionally feels tired during his senior year of college but is otherwise asymptomatic. You first saw him 6 weeks ago and noted a harsh, holosystolic murmur at the left lower sternal border that augmented with hand grip. Suspecting a ventricular septal defect (VSD), you referred him for echocardiography, which confirmed your suspicion, visualizing a 5-mm VSD in the muscular interventricular septum. Subsequent right heart catheterization for hemodynamic assessment revealed a mean pulmonary artery pressure of 20 mmHg, pulmonary venous resistance of 2 Wood units, and systemic vascular resistance of 6 Wood units. Through meticulous serial measurements of venous oxygen saturations in the central veins and right heart, you calculate a right heart cardiac output of 7.5 L/min and systemic cardiac output of 6 L/min. Given these findings, you recommend what therapeutic course?
- A. Cardiopulmonary exercise testing to define peak oxygen consumption
- B. Closure with a percutaneously deployed septal occluder device
- C. Consideration of heart and lung transplant
- D. No intervention now; annual cardiology assessments and reimaging if any new symptoms emerge
- E. Surgical correction via open heart surgery and patch repair
- 77.** You are evaluating a 52-year-old patient who presented to the emergency department for chest pain and elevated cardiac enzymes. On auscultation, you can easily hear a superficial, continuous murmur at the mid-sternal level that was never documented before. Echocardiography is limited but is able to visualize all the cardiac valves, which appear completely normal. The patient undergoes a right heart catheterization. The oxygen saturation values are shown below. What is the abnormality accounting for this patient's symptoms?
- | | |
|--------------------|-----|
| Superior vena cave | 58% |
| Right atrium | 60% |
| Mid-coronary sinus | 91% |
| Right ventricle | 70% |
| Pulmonary artery | 70% |
- A. Anomalous left coronary artery off the main pulmonary artery
- B. Atrial septal defect
- C. Coronary arteriovenous fistula to the coronary sinus
- D. Patent ductus arteriosus
- E. Ventricular septal defect
- 78.** Mr. Jenson is a 40-year-old man with a congenital bicuspid aortic valve who you have been seeing for more than a decade. You obtain an echocardiogram every other year to follow the progression of his disease knowing that bicuspid valves often develop stenosis or regurgitation requiring replacement in middle age. Given his specific congenital abnormality, what other anatomic structure is important to follow on his biannual echocardiograms?
- A. Aortic root size
- B. Left atrial size
- C. Pulmonary artery pressures
- D. Pulmonic valve function
- E. Tricuspid valve regurgitation
- 79.** All of the following are classic definitional features of the tetralogy of Fallot EXCEPT:
- A. Obstruction to RV outflow
- B. Overriding aorta
- C. RV hypertrophy
- D. Tricuspid atresia
- E. Ventricular septal defect
- 80.** A 78-year-old man is evaluated for the onset of dyspnea on exertion. He has a long history of tobacco abuse, obesity, and diabetes mellitus. His current medications include metformin, aspirin, and occasional ibuprofen. On physical examination, his peripheral pulses show a delayed peak, and he has a prominent left ventricular heave. He is in a regular rhythm with a IV/VI mid-systolic murmur, loudest at the base of the heart and radiating to the carotid arteries. A fourth heart sound is present. Echocardiography confirms severe aortic stenosis without other valvular lesions.

Which of the following most likely contributed to the development of his cardiac lesion?

- A. Congenital bicuspid aortic valve
- B. Diabetes mellitus
- C. Occult rheumatic heart disease
- D. Underlying connective tissue disease
- E. None of the above

81. A 63-year-old man presents with new-onset exertional syncope and is found to have aortic stenosis. In counseling the patient, you tell him that your therapeutic recommendation is based on the observation that untreated patients with his presentation have a predicted average life span of:

- A. 5 years
- B. 4 years
- C. 3 years
- D. 2 years
- E. 1 year

82. Mr. Belliard is an 82-year-old man whom you previously followed in clinic. He was last seen 3 years ago, when he noted occasional syncope. Subsequent workup revealed severe calcific aortic stenosis with an aortic valve area of 0.7 cm^2 and mean gradient of 45 mmHg. At that time, you recommended surgical aortic valve replacement. On the day of his operation, however, Mr. Belliard called to say he really did not feel quite sick enough to undergo open heart surgery, and he would be back in touch when he was ready. He missed all subsequent follow-up appointments. Today, he presents to the emergency department after several weeks of lethargy and dyspnea. His blood pressure is 82/68 mmHg and heart rate is 110 bpm, and he has an ECG showing sinus rhythm. His carotid impulse is weak and delayed, and extremities are cool to the touch. You again appreciate an S_4 on auscultation and a III/VI late-peaking systolic murmur. His renal and liver function are now impaired, and urine output is poor. The cardiothoracic surgeon on call defers emergent surgical valve replacement due to his acute renal and hepatic injury. Which of the following would be a reasonable therapeutic option to improve Mr. Belliard's short-term perfusion to permit aortic valve replacement?

- A. Atorvastatin 80 mg
- B. Digoxin 250 μg IV once and 125 μg orally daily thereafter
- C. Metoprolol 5 mg IV serial dosing targeting a resting heart rate of 60–70 bpm
- D. Percutaneous aortic balloon valvuloplasty
- E. Phenylephrine continuous IV infusion titrated to a mean arterial pressure of $>65 \text{ mmHg}$

83. An 85-year-old former lawyer presents with several months of accelerating dyspnea on exertion and lower extremity edema. On examination, you note a laterally displaced point of maximal impulse (PMI) and an S_4 gallop. She has a III/VI systolic murmur at the base

radiating to the carotid arteries. Transthoracic echocardiogram reveals a left ventricular ejection fraction of 25% with global hypokinesis. Calculated aortic valve area is 0.8 cm^2 and mean gradient is 25 mmHg. What is the next most reasonable step to determine whether this patient would benefit from aortic valve replacement?

- A. Cardiac magnetic resonance imaging (MRI) to evaluate ventricular scar and aortic valve morphology
- B. Cardiac positron emission tomography (PET) to determine ventricular viability
- C. Coronary angiography to evaluate for the presence of obstructive coronary disease
- D. Dobutamine stress echocardiography
- E. Right heart catheterization to document cardiac output and filling pressures

84. Which of the following parameters is typically reduced in chronic severe aortic regurgitation?

- A. Diastolic blood pressure
- B. Left ventricular afterload
- C. Left ventricular diameter
- D. Left ventricular preload
- E. Total left ventricular stroke volume

85. You are caring for a new admission to the cardiac intensive care unit, a 21-year-old woman with connective tissue disease. She presented with acute shortness of breath and a chest x-ray showing diffuse pulmonary edema. Physical examination revealed a soft, short early diastolic murmur at the right upper sternal border, and emergent echocardiography showed severe aortic regurgitation with an avulsed right coronary cusp. CT chest imaging showed no aortic dissection. On arrival to the coronary care unit, she is intubated and sedated. Blood pressure is 110/50 mmHg and heart rate is 115 bpm. Her urine output is poor and extremities are cool. The cardiothoracic surgical team is tied up in a heart transplant and will not be able to take this patient for at least 4 more hours. What intervention is most likely to help maintain her end-organ perfusion until surgical intervention?

- A. Esmolol continuous IV infusion titrated to a heart rate of 60–70 bpm
- B. Intra-aortic balloon pump
- C. IV nitroprusside
- D. IV norepinephrine
- E. IV vasopressin

86. What is the most common cause of obstruction to left ventricular inflow?

- A. Congenital mitral valve disease
- B. Cor triatriatum
- C. Infective endocarditis with large mitral valve vegetations
- D. Mitral annular calcification
- E. Rheumatic mitral disease

87. In cases of severe mitral stenosis, which of the following parameters is typically increased?
- Cardiac output
 - Left atrial pressure
 - Left ventricular diameter
 - Left ventricular end-diastolic pressure
 - Pulmonary vascular compliance
88. You are caring for a 42-year-old woman with a prior history of rheumatic fever and resultant mitral stenosis. Her valvular disease is currently moderate. You know that mitral stenosis causes an elevation in left atrial pressure, which over time can cause cardiogenic pulmonary edema and pulmonary hypertension. All of the following will result in an elevation of left atrial pressure and potential worsening of lung function EXCEPT:
- Anemia
 - Isoproterenol
 - Metoprolol
 - Pregnancy
 - Running on a treadmill
89. Mrs. Bream presents to the emergency department with acute worsening of shortness of breath. She is an 84-year-old woman with severe mitral stenosis who is scheduled for percutaneous mitral balloon valvotomy in 3 days. However, today while cooking chicken salad, she noted the onset of overwhelming weakness and dyspnea. On evaluation, she appears dyspneic and in mild distress. Oxygen saturation on room air is 91%, heart rate is 55 bpm, and blood pressure is 110/80 mmHg. She has rales to the mid-lung fields bilaterally. You note that her rhythm is irregularly irregular, and ECG confirms the new onset of atrial fibrillation. You suspect that she has a very high left atrial pressure causing pulmonary edema. All of the following therapeutic interventions will help lower her left atrial pressure EXCEPT:
- IV furosemide
 - Percutaneous balloon mitral valvotomy
 - Synchronized DC cardioversion
 - Transvenous pacemaker placement and pacing at a heart rate of 90 bpm
 - All of the above will help lower left atrial pressure
90. A 34-year-old man with rheumatic mitral stenosis is referred to you for evaluation. He enjoys playing recreational soccer and has no limitations or symptoms. His heart rate is 65 bpm at rest. Transthoracic echocardiogram reveals a normal LV size and function, a moderately dilated left atrium, a mitral valve area of 1.7 cm^2 , and relatively thin noncalcified leaflets. ECG shows left atrial enlargement and sinus rhythm. On exercise stress testing, his calculated pulmonary artery systolic pressure at peak exercise is 40 mmHg. Which of the following treatment plans do you recommend?
- Metoprolol 25 mg orally twice daily
 - Percutaneous mitral balloon valvotomy
 - Periodic cardiology assessments and echocardiographic monitoring
 - Sildenafil 20 mg twice daily
 - Surgical mitral valve replacement
91. You are evaluating a 65-year-old man who has a 15-year history of nonischemic cardiomyopathy with a dilated left ventricle and an ejection fraction of 15%. Yearly echocardiograms over the past 5 years have shown severe mitral regurgitation. On optimal medical therapy, the patient has NYHA class II symptoms. Today, he specifically asks whether his valve should be fixed in order to improve his survival. You should tell him:
- “If you were to have high pulmonary artery pressures or develop new atrial fibrillation, we would move forward with valve repair.”
 - “In patients like you, valve repair has never been shown to improve survival.”
 - “We should consider valve surgery only if repair is possible. Replacement would not improve your survival.”
 - “While surgical methods have not shown survival benefit, percutaneous mitral valve repair has been shown to reduce mortality in patients like you.”
 - “Yes, your valve should have been fixed years ago.”
92. You are performing a right and left heart catheterization on a patient with stenosis involving two valves. Which two valves are involved based on the pressure readings listed below?
- | | |
|-----------------------------------|-------------|
| Right atrium | 15 mmHg |
| Right ventricle | 25/6 mmHg |
| Pulmonary artery | 25/12 mmHg |
| Pulmonary arterial wedge pressure | 12 mmHg |
| Left ventricle | 105/6 mmHg |
| Aorta | 105/75 mmHg |
- Aortic and mitral
 - Aortic and tricuspid
 - Mitral and pulmonic
 - Mitral and tricuspid
 - Pulmonic and tricuspid
93. You are evaluating a 50-year-old woman with idiopathic pulmonary arterial hypertension. Her last transthoracic echocardiogram noted severe tricuspid regurgitation in addition to a dilated hypokinetic right ventricle and estimated pulmonary artery systolic pressures exceeding 70 mmHg. On your examination, she has lower extremity edema, hepatomegaly with a pulsatile liver, jugular venous pulse elevated to the mandible with marked c-v waves and a prominent y descent, and an RV heave. She reports breathlessness with moderate exertion. What is the best treatment for her severe tricuspid regurgitation?

- A. Diuretics and salt restriction accompanied by medical therapy targeting her elevated pulmonary artery pressures
 - B. Percutaneous balloon valvotomy
 - C. Percutaneous tricuspid valve repair
 - D. Surgical mitral valve replacement
 - E. Surgical tricuspid valve repair
- 94.** You are seeing a 21-year-old woman for the first time today in the primary care clinic. She has never seen a physician before because her parents did not believe in Western medicine. On history, she states that she feels tired occasionally and feels like she could not quite keep up with her peers in college physical education classes. On examination, you note a systolic murmur in the left second interspace preceded by a presystolic click. Transthoracic echocardiogram confirms the presence of pulmonic stenosis with a peak gradient of 60 mmHg and doming of the pulmonic valve without any pulmonic regurgitation. What is her best treatment option?
- A. Diuretics and salt restriction
 - B. No therapy needed
 - C. Percutaneous balloon valvotomy
 - D. Percutaneous pulmonic valve replacement
 - E. Surgical pulmonic valve replacement
- 95.** You are taking care of a 77-year-old patient with severe aortic stenosis in the cardiac intensive care unit. Surgical aortic valve replacement is planned for tomorrow. However, suddenly, he becomes severely short of breath and manifests signs of acute pulmonary edema. On auscultation, you can now appreciate a soft, short apical systolic murmur (in addition to his previously appreciated murmur of aortic stenosis) that was not present previously. You suspect that he has suffered a ruptured mitral valve chordae and now has severe, acute mitral regurgitation. Which of the following parameters will likely increase due to his new severe mitral regurgitation?
- A. Aortic valve gradient
 - B. Calculated aortic valve area
 - C. Effective stroke volume
 - D. Ejection fraction
 - E. Left ventricular afterload
- 96.** Mr. Milsap is one of your longstanding clinic patients who has a history of rheumatic heart disease. His last echocardiogram noted a mean mitral valve gradient of 11 mmHg with a calculated valve area of 1.3 cm^2 at a heart rate of 60 bpm. He presents today complaining of worsening shortness of breath, and his ECG shows atrial fibrillation at a rate of 60 bpm. He has never had any bleeding episodes and had normal hematologic counts on his last check 2 weeks earlier. Which of the following options for thromboembolic prophylaxis is appropriate?
- A. Apixaban
 - B. Dabigatran
 - C. Rivaroxaban
 - D. Warfarin
 - E. More information is needed prior to initiating thromboembolic prophylaxis.
- 97.** All of the following are risk factors for development of peripartum cardiomyopathy EXCEPT:
- A. Advanced maternal age
 - B. Malnutrition
 - C. Primiparous
 - D. Twin pregnancy
 - E. Use of tocolytics
- 98.** You are evaluating a new patient in clinic. The 25-year-old patient was diagnosed with “heart failure” in another state and has since relocated. He has NYHA class II symptoms and denies angina. He presents for evaluation and management. On review of systems, the patient has been wheelchair bound for many years and has severe scoliosis. He has no family history of hyperlipidemia. His physical examination is notable for bilateral lung crackles, an S_3 , and no cyanosis. An ECG is obtained in clinic and shows tall R waves in V_1 and V_2 with deep Qs in V_5 and V_6 . An echocardiogram reports severe global left ventricular dysfunction with reduced ejection fraction. What is the most likely diagnosis?
- A. Amyotrophic lateral sclerosis
 - B. Atrial septal defect
 - C. Chronic thromboembolic disease
 - D. Duchenne muscular dystrophy
 - E. Ischemic cardiomyopathy
- 99.** Which of the following is the most common inheritance pattern for familial cardiomyopathies?
- A. Autosomal dominant driven by exon duplication
 - B. Autosomal dominant driven by missense mutations
 - C. Autosomal recessive driven by exon deletion
 - D. Autosomal recessive driven by exon duplication
 - E. X-linked driven by exon deletion
- 100.** A 45-year-old man with a history of obesity presents to the emergency department with dyspnea, fatigue, and a nocturnal cough that has been worsening for the past several months. He denies any chest pain or pressure at rest or with exertion. On evaluation, he has evidence of cardiomegaly with a displaced PMI and elevated filling pressures with bilateral pulmonary rales and elevated jugular venous pulse. Echocardiography reveals a globally depressed left ventricular ejection fraction of 25% with a dilated left ventricle. Which of the following tests is a level I recommendation for further workup?
- A. Cardiac MRI
 - B. Coronary angiography
 - C. Erythrocyte sedimentation rate
 - D. Serum iron and transferrin saturation
 - E. Thyroid-stimulating hormone level
- 101.** A 22-year-old college student with no past medical history was seen in the urgent care clinic 3 days ago for coryza, myalgias, cough, and fever, which was typical of the viral upper respiratory illness making its way through the campus. He

was given a cough suppressant and antipyretics and advised to remain hydrated. Today, he presents to the emergency department with lethargy and fatigue. He is obtunded with a heart rate of 120 bpm and blood pressure of 78/62 mmHg. His extremities are cool, and jugular venous pulse is elevated nearly to the mandible. Precordial auscultation reveals very quiet heart sounds, an S_3 gallop, and a soft murmur of mitral regurgitation. Emergent transthoracic echocardiogram shows no pericardial effusion, a nondilated left ventricle with an ejection fraction of 30%, and mild mitral regurgitation. Endomyocardial biopsy shows lymphocytic myocarditis. Which of the following statements regarding this patient's prognosis and implications for therapy are true?

- A. His chance of survival is <10% without cardiac transplantation. Emergent transplant listing is warranted.
 - B. His chance of survival is >50%, with many similar patients having a full recovery in left ventricular function over the ensuing weeks to months. Aggressive pharmacologic and mechanical hemodynamic support is warranted.
 - C. Immunosuppression with high-dose systemic steroids will increase his chance of survival.
 - D. The presence and titer of anti-heart antibodies can help provide prognostic information for this patient.
- 102.** You are evaluating a 42-year-old woman with a history of Hashimoto thyroiditis many years ago who was treated successfully with radioactive iodine. She presents to the emergency department after passing out at home and reports several days of worsening lethargy and chest discomfort. She is short of breath with a resting heart rate of 110 bpm and blood pressure of 77/62 mmHg. Her extremities are cool, and she seems sleepy. Her whole blood lactate is elevated, and urine output for the first 2 hours of her stay is minimal. On cardiac monitor, she repeatedly has salvos of nonsustained ventricular tachycardia. Echocardiogram reveals a left ventricular ejection fraction of 15%, and emergent endomyocardial biopsy shows diffuse granulomatous lesions surrounded by extensive inflammatory infiltrate. Which of the following statements is true regarding her diagnosis?

- A. Most patients with this etiology of cardiomyopathy recover with supportive care.
- B. Steroids are highly effective in treating this form of cardiomyopathy.
- C. The course of this cardiomyopathy is dire, often with rapid deterioration requiring urgent transplantation.
- D. While seen occasionally, ventricular tachyarrhythmias are rare in this disease.
- E. None of the above is true.

103. All of the following are associated with an elevated risk for development of cardiomyopathy during anthracycline chemotherapy EXCEPT:

- A. Concomitant chest radiation
- B. High total anthracycline dose
- C. Preexisting cardiac disease
- D. Trastuzumab administration
- E. All of the above are associated with elevated risk of cardiomyopathy due to anthracyclines.

104. Mr. Kia is a 32-year-old bass guitarist with no past medical history. He presents with chest pain after suffering coryza, cough, fever, and muscle aches for the past week. He describes his pain as constant and radiating to his left shoulder. It is exacerbated by lying flat and during deep breaths. Examination reveals a rasping extracardiac sound present in three components per heartbeat. His ECG is shown in Figure 23. Troponin I levels are undetectable on presentation and 6 hours later. Blood pressure, heart rate, and oxygenation are normal. What is the most appropriate next step?

- A. Aspirin 81 mg daily, metoprolol 25 mg twice daily, and atorvastatin 80 mg daily
- B. Aspirin 1 g every 8 hours with omeprazole 20 mg daily
- C. Heparin, aspirin, clopidogrel, and immediate coronary angiography
- D. Prednisone 40 mg daily for 2 weeks followed by a taper over the ensuing 2 months
- E. Transthoracic echocardiogram

105. You are caring for a 45-year-old man in the cardiac intensive care unit. He presented with chest pain and initially

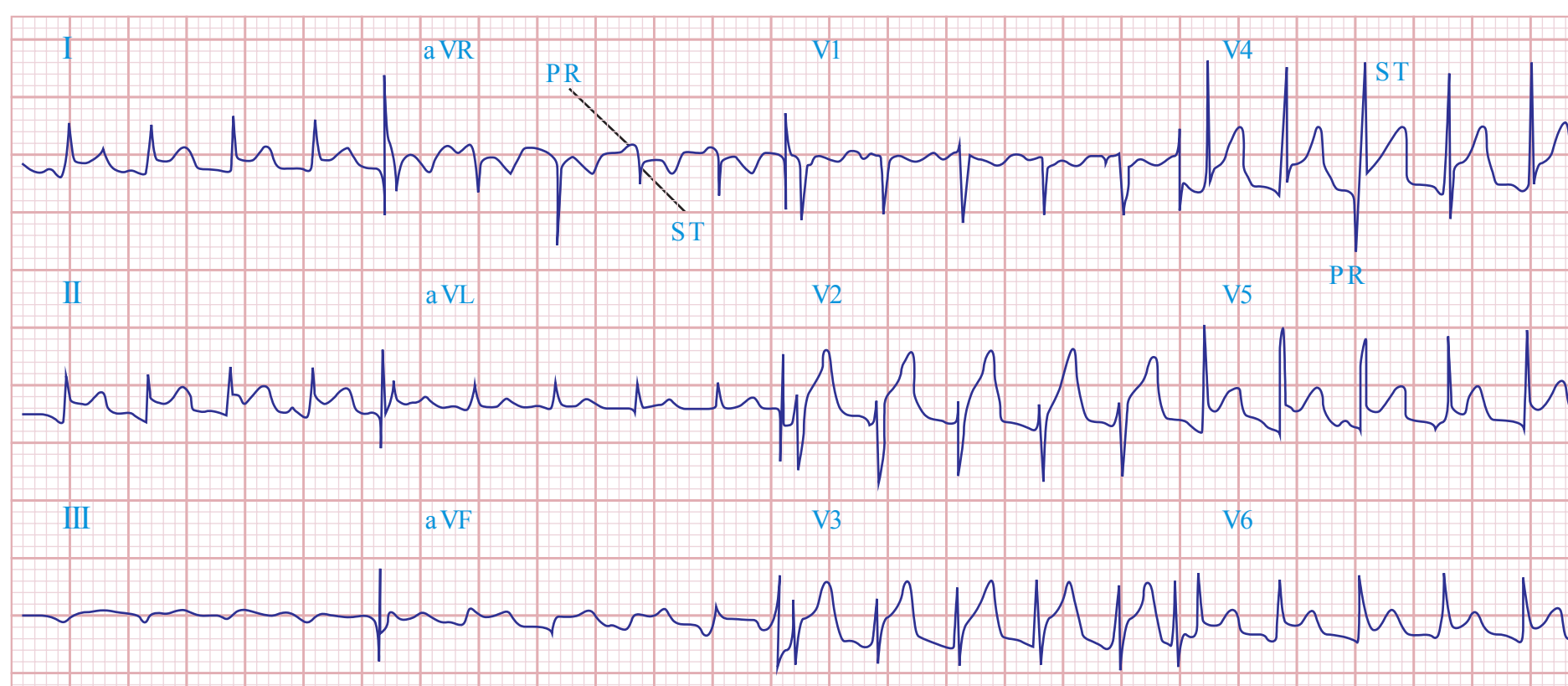


FIGURE 23

was thought to have acute coronary syndrome, prompting initiation of antiplatelet agents and IV heparin. After complete assessment and the return of negative serial cardiac enzymes, it became clear that he instead had acute pericarditis. Shortly after admission to the cardiac intensive care unit, he becomes hypotensive with elevated neck veins. His lungs are clear to auscultation. His extremities are cool, and you note that his brachial pulse is only palpable during expiration. What is the most likely diagnosis?

- A. Aortic dissection
- B. Cardiac tamponade
- C. Left main coronary artery occlusion
- D. Ruptured chordae tendineae
- E. Ventricular septal defect

106. You call for emergent echocardiography in the patient described in Question 106. In this patient, which of the following is likely to be increased during inspiration compared to expiration?

- A. Left ventricular end-diastolic diameter
- B. Left ventricular stroke volume
- C. Mitral inflow velocity
- D. Systolic blood pressure
- E. Tricuspid inflow velocity

107. All of the following ECG characteristics will aid in differentiating acute pericarditis from acute myocardial infarction EXCEPT:

- A. Absence of the development of Q waves
- B. Concave shape to ST elevations
- C. PR depression
- D. ST elevation in V₂
- E. T-wave inversions after return of the ST segments to baseline

108. A 35-year-old woman is admitted to the hospital with malaise, weight gain, increasing abdominal girth, and edema. The symptoms began about 3 months ago and gradually progressed. The patient reports an increase in waist size of approximately 15 cm. The swelling in her legs has gotten increasingly worse such that she now feels her thighs are swollen as well. She has dyspnea on exertion and two-pillow orthopnea. She has a past history of Hodgkin disease diagnosed at age 18. She was treated at that time with chemotherapy and mediastinal irradiation. On physical examination, she has temporal wasting and appears chronically ill. Her current weight is 96 kg, an increase of 11 kg over the past 3 months. Her vital signs are normal. Her jugular venous pressure is ~16 cm, and the neck veins do not collapse on inspiration. Heart sounds are distant. There is a third heart sound heard shortly after aortic valve closure. The sound is short and abrupt and is heard best at the apex. The liver is enlarged and pulsatile. Ascites is present. There is pitting edema extending throughout the lower extremities and onto the abdominal wall. Echocardiogram shows

pericardial thickening, dilatation of the inferior vena cava and hepatic veins, and abrupt cessation of ventricular filling in early diastole. Ejection fraction is 65%. What is the best approach for treatment of this patient?

- A. Aggressive diuresis only
- B. Cardiac transplantation
- C. Mitral valve replacement
- D. Pericardial resection
- E. Pericardiocentesis

109. A 45-year-old accountant with no prior past medical history has experienced occasional fevers, symmetric arthralgias, and fatigue for the past 3 months. Two weeks ago, she experienced the sudden onset of left hand weakness, which resolved within 1 hour. Multiple blood cultures have been negative. Emergent evaluation at her local emergency department included a head CT that was unrevealing. Last week, she had a transthoracic echocardiogram that showed a solitary, 2-cm mass in the left atrium arising from the interatrial septum in the vicinity of the fossa ovalis that appeared pedunculated on a fibrovascular stalk. You are seeing her back in clinic today. What is the most appropriate next step?

- A. Cardiothoracic surgical removal of the mass
- B. Catheter-based biopsy of the mass
- C. Repeat blood cultures and inform the microbiology laboratory to plate on special media to evaluate for HACEK organisms
- D. Serologies for antinuclear antibodies (ANAs), anti-DNA, and anticardiolipin antibodies
- E. Whole-body PET scan to evaluate for malignancy

110. Which of the following malignancies carries the highest relative risk of metastasis to the heart?

- A. Glioblastoma
- B. Hepatocellular carcinoma
- C. Malignant melanoma
- D. Pancreatic adenocarcinoma
- E. Small-cell lung cancer

111. You are attending your 12-year-old son's Little League baseball game. The score is tied 2–2 in the ninth inning, and your son's team is up to bat. On the first pitch of the inning, the batter fouls the ball directly back into the catcher's chest. The catcher immediately loses consciousness and collapses. He is pulseless with agonal respirations. You, as a physician, know that his survival depends most on which of the following?

- A. Emergent transfer to a cardiac catheterization laboratory for percutaneous coronary intervention
- B. Emergent transfer to a trauma center for repair of an acute aortic dissection
- C. No intervention can impact this patient's survival
- D. Prompt cardiac surgery to repair an avulsed aortic valve
- E. Prompt defibrillation

- 112.** A 47-year-old woman with a body mass index (BMI) of 37 kg/m^2 was recently diagnosed with type 2 diabetes mellitus. As part of her patient education, you inform her that which of the following is the most common cause of death in adults with type 2 diabetes mellitus?
- Coronary artery disease
 - Infection
 - Neuropathy
 - Renal failure
 - Stroke
- 113.** Mr. Daniels is a 49-year-old man known well to your emergency department for frequent visits for alcohol intoxication. As the on-call internal medicine house officer, you are called to evaluate him for admission tonight. On arrival, he is only mildly intoxicated and able to provide a passable history. He claims that for the past 3 months, he has been increasingly short of breath with even minimal exertion and is experiencing overwhelming fatigue. He has also been awakening at night with extreme shortness of breath only alleviated by sitting on the edge of his bed. His ankles have been swollen. On examination, his blood pressure is 140/45 mmHg and heart rate is 122 bpm. He has a bounding carotid pulse and elevated jugular venous pulse. His PMI is laterally displaced, and you clearly hear a low-pitched cardiac sound directly following the S_2 . You note glossitis and find that he lacks sensation to light touch below the mid-shins bilaterally. Basic laboratory studies are notable for an albumin of 3.2 g/dL, creatinine of 1.4 mg/dL, and sodium of 134 mEq/L. Transthoracic echocardiogram reveals a left ventricular end-diastolic dimension of 6.8 cm with an ejection fraction of 70%.
- You adroitly make the diagnosis and administer a substance to treat the underlying cause of Mr. Daniels's condition. Reassessment in 24 hours finds him symptomatically improved with a blood pressure of 142/76 mmHg and heart rate of 85 bpm. Repeat echocardiogram now shows his LV size to be 6.2 cm in end-diastole. Which of the following most likely caused Mr. Daniels's condition to improve so rapidly?
- Folate
 - Penicillamine
 - Tiamine
 - Tyroxine
 - Vitamin B_{12}
- 114.** A 65-year-old former factory worker with a past medical history of rheumatoid arthritis presents to your primary care clinic complaining of fatigue. She also states that she has the following symptoms: constipation, constantly feeling cold even when the thermostat is set on 80°F, brittle hair, and some lower extremity swelling. You expeditiously measure her thyroid-stimulating hormone, which is greatly elevated at 79.4 mIU/L. In regard to the present condition of her cardiovascular system, you expect a decrease in all of the following measurements EXCEPT:
- Cardiac output
 - Heart rate
 - Pulse pressure
 - QT interval
 - Systolic blood pressure
- 115.** In the current model describing the steps of atherosclerosis initiation and evolution, which of the following constitutes the first step?
- Arterial endothelial cells overexpress adhesion receptors for leukocytes.
 - Lipoprotein particles undergo oxidative modifications.
 - Low-density lipoproteins accumulate within the arterial intima.
 - Macrophages and other leukocytes are recruited to the arterial intima.
 - Macrophages become lipid-laden foam cells via endocytosis of lipoprotein particles.
- 116.** Which of the following statements regarding the pathophysiologic consequences of an atheroma is true?
- An atheroma resulting in total vascular occlusion invariably causes infarction.
 - An enlarging atheroma does not generally encroach on the arterial lumen until the plaque exceeds 40% of the internal elastic lamina.
 - Most atheromas will eventually produce symptoms in the patient.
 - Upon initial formation, the atheromatous plaque usually grows inward toward the vessel lumen.
 - Vessels affected by atherogenesis tend to contract and get smaller in diameter.
- 117.** Based on the 2013 cholesterol guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA), all of the following groups are a definite statin benefit group EXCEPT:
- All individuals who have clinical atherosclerotic cardiovascular disease (ASCVD)
 - Individuals with an elevated high-sensitivity C-reactive protein (CRP) regardless of low-density lipoprotein (LDL) cholesterol level or ASCVD risk
 - Individuals with LDL cholesterol $\geq 190 \text{ mg/dL}$ without a secondary cause such as a high intake of saturated or trans fats or various drugs
 - Individuals without established ASCVD or diabetes who are 40–75 years old and who have LDL cholesterol of 70–189 mg/dL and a calculated ASCVD risk $\geq 7.5\%$
 - Patients with diabetes without established cardiovascular disease who are 40–75 years old and have LDL cholesterol of 70–189 mg/dL

- 118.** A 50-year-old man presents to your clinic for his yearly check-up. Today, he is quite concerned about his future risk for heart attack and stroke after having read some concerning news articles in print and online. He has a history of vascular disease. He has gained some weight over the last decade, and his BMI today is 34 kg/m^2 . His lipid panel is below:

Total cholesterol	220 mg/dL
Triglycerides	283 mg/dL
High-density lipoprotein (HDL)	29 mg/dL
LDL	132 mg/dL

You calculate his ASCVD risk as 6% with the risk calculator provided by the ACC/AHA. The patient has read that his low HDL cholesterol has been identified as correlated with his risk of future cardiovascular disease. He wants to know what you can prescribe in regard to his HDL that will definitively lower his cardiovascular risk to the largest degree. What is the correct answer?

- A. An agonist of peroxisome proliferator-activated receptor α
 - B. An inhibitor of cholesteryl ester transfer protein
 - C. Fenofibrate
 - D. Nicotinic acid
 - E. Weight loss and physical activity
- 119.** All of the following are major determinants of myocardial oxygen demand EXCEPT:
- A. Heart rate.
 - B. Heart rhythm.
 - C. Myocardial contractility.
 - D. Ventricular wall stress.
 - E. All of the above are major determinants of myocardial oxygen demand.
- 120.** Mr. Jackson is undergoing an exercise stress test. You know that as he progresses through his stress test, his myocardium will require more oxygen. How does the normal (nondiseased) heart respond to meet its higher oxygen demand?
- A. Increased myocardial oxygen extraction during near-constant coronary blood flow
 - B. Increased oxygen extraction from the ventricular chambers
 - C. Relative expansion of the diastolic time period allowing increased coronary flow
 - D. Vasodilation of epicardial coronary arteries leading to decreased resistance and increased coronary blood flow
 - E. Vasodilation of intramyocardial coronary vessels leading to increased coronary blood flow

- 121.** As Mr. Jackson (from Question 120) continues on his exercise stress test, he begins to complain of a pressure-like chest pain. You suspect that he is experiencing angina due to a partially occluded coronary artery. If you were able to immediately analyze the biochemical changes occurring in his ischemic myocardium, you would note all of the following EXCEPT:

- A. An increase in cytosolic calcium
- B. An increase in intracellular pH
- C. A shift from aerobic to anaerobic metabolism
- D. Depletion of myocardial stores of high-energy phosphates
- E. Leakage of potassium from myocytes

- 122.** Which of the following sites is an unusual anatomic location for anginal pain radiation?

- A. Back
- B. Interscapular region
- C. Root of the neck
- D. Teeth
- E. Trapezius muscle

- 123.** Ms. Wilson is a 66-year-old postmenopausal U.S. postal employee. While walking her mail route over the past 9 months, she has routinely experienced chest pressure and dyspnea while climbing a certain steep hill. The pressure resolves when she rests for about 3 minutes. She has not missed any work due to these symptoms. You suspect she is experiencing angina. What term and Canadian Cardiovascular Society (CCS) Functional Class of angina is appropriate to describe her symptoms?

- A. Stable angina – CCS class I
- B. Stable angina – CCS class II
- C. Stable angina – CCS class III
- D. Stable angina – CCS class IV
- E. Unstable angina

- 124.** A 50-year-old accountant with a history of cigarette use completed an exercise treadmill ECG stress test. During his test, he developed upsloping ST depressions in leads II, III, and aVF. His peak heart rate achieved was 130 bpm. His blood pressure increased from 120/80 to 155/95 mmHg. What is the appropriate interpretation of this stress test?

- A. Negative stress test; inappropriate hypertensive response to exercise
- B. Negative stress test; nonspecific ST changes
- C. Nondiagnostic stress test; normal blood pressure response
- D. Positive stress test; inappropriate hypertensive response to exercise
- E. Positive stress test; normal blood pressure response

- 125.** A 70-year-old woman presents to the emergency department with 3 hours of acute shortness of breath and crushing substernal chest pressure. Her ECG shows 1-mm ST

depression in leads II, III, and aVF without any ST elevation. Initial serum troponin level is mildly elevated. You suspect that she is having a non-ST-segment elevation myocardial infarction (NSTEMI). All of the following are causes of NSTEMI EXCEPT:

- A. Coronary vasospasm
- B. Increased myocardial oxygen demand produced by systemic conditions
- C. Microvascular endothelial dysfunction
- D. Partially occluding thrombus forming on disrupted atherothrombotic coronary plaque
- E. Progressive coronary atherosclerosis leading to severe mechanical obstruction

126. Mr. Brian is a 57-year-old hockey team coach with a prior history of hypertension, hyperlipidemia, and tobacco abuse. He presents to the emergency department tonight after experiencing chest discomfort during a practice. He notes that he first began experiencing chest discomfort 3 weeks prior with vigorous exertion during practice. However, over the last week, it has taken less exertion to initiate the discomfort. Tonight, it occurred while he was just sitting on the bench. He describes the discomfort as a pressure, radiating to his jaw. It typically lasts about 10 minutes. His ECG shows new T-wave inversions in leads I, II, aVL, V₅, and V₆ because his last cardiogram 2 years ago at a routine physical examination. Which of the following clinical entities is an appropriate diagnosis for Mr. Brian?

- A. Non-ST-segment elevation myocardial infarction
- B. ST-segment elevation myocardial infarction
- C. Stable angina
- D. Unstable angina
- E. More information is required before making a diagnosis.

127. Mr. Riviera is a 42-year-old man with anuric end-stage renal disease due to diabetes mellitus. Due to recent car trouble, he missed his most recent dialysis appointment and presents to the emergency department with shortness of breath. His heart rate is 105 bpm and blood pressure is 185/100 mmHg. He has fine rales in the bilateral lower lung fields, and his jugular venous pulse is elevated. ECG shows sinus tachycardia without ST deviation. Initial troponin I assay returns at 0.14 ng/dL (normal is <0.06 ng/dL). What are the next most appropriate therapeutic and diagnostic steps?

- A. Administer 80 mg of IV furosemide. Follow serial troponin I values and ECGs.
- B. Administer 80 mg of aspirin. Refer for pharmacologic nuclear stress testing.
- C. Initiate dual antiplatelet therapy (aspirin and clopidogrel) and heparin. Follow serial troponin I values and ECGs.
- D. Initiate dual antiplatelet therapy (aspirin and clopidogrel) and heparin. Refer for urgent coronary angiography.
- E. Initiate urgent hemodialysis with ultrafiltration for fluid removal. Follow serial troponin I values and ECGs.

128. A 67-year-old fry chef at the local Waffle Emporium presents to the emergency department with the sudden onset of crushing substernal chest pain. He has a history of hypertension, hyperlipidemia, and erectile dysfunction for which he takes daily amlodipine, simvastatin, and tadalafil. On your evaluation, his blood pressure is 145/85 mmHg and heart rate is 90 bpm. His lungs are clear and jugular venous pulse is not elevated. There are no murmurs or gallops on cardiac auscultation. He continues to complain of chest discomfort, rating it an 8/10. Initial troponin I result is elevated at 0.52 ng/dL (normal <0.06 ng/dL), and ECG reveals 1-mm ST depression in leads II, III, aVF, V₅, and V₆. All of the following pharmacologic therapies are reasonable to administer EXCEPT:

- A. Aspirin orally
- B. Clopidogrel orally
- C. Heparin intravenously
- D. Metoprolol intravenously
- E. Nitroglycerin sublingually

129. Mr. Gilotra is a 57-year-old oil rig worker with a history of hypertension, tobacco abuse, and diabetes mellitus. He presents to the emergency department with 30 minutes of crushing substernal chest pain radiating to the jaw and associated with profuse sweating and shortness of breath. His blood pressure is 115/90 mmHg and heart rate is 95 bpm. What diagnostic test will provide the most rapid method of altering therapeutic management for Mr. Gilotra?

- A. 12-lead ECG
- B. Coronary CT angiography
- C. Echocardiogram
- D. Serum creatine kinase-MB (CK-MB) band level
- E. Serum troponin I level

130. You are evaluating a patient with chest pain in the emergency department. The ECG shows no Q waves or ST-segment changes. You wish to know whether the patient is suffering a myocardial infarction. Which of the following biomarkers is the preferred biochemical marker of myocardial infarction?

- A. Creatine kinase
- B. CK-MB band
- C. Erythrocyte sedimentation rate
- D. Lactate dehydrogenase
- E. Troponin I

131. You are performing a diagnostic coronary angiography on Mr. Hayes. On the initial angiographic pictures, his arteries are clear of any obstructive disease. However, during a selective angiogram of the left anterior descending artery, you notice that a thrombus has formed on the tip of your catheter. During dye injection, the thrombus embolizes down the left anterior descending coronary artery causing complete obstruction to flow. Fortunately, you are able to remove the thrombus with suction thrombectomy almost immediately. If you had not been able to remove the

thrombus, when would you first have expected detectable CK-MB isoform in a standard serum assay?

- A. 5–10 minutes
- B. 1–2 hours
- C. 4–8 hours
- D. 12–24 hours
- E. 24–48 hours

132. The greatest delay between symptom onset and definitive therapy for patients with ST-segment elevation myocardial infarction usually occurs in what time interval?

- A. Between onset of pain and patient's decision to call for help
- B. Between patient call and emergency medical team arrival
- C. Between emergency medical team arrival and arrival at the hospital
- D. Between arrival at the hospital and decision to initiate reperfusion therapy
- E. Between decision to initiate reperfusion therapy and the actual initiation of this therapy

133. All of the following medications used in the acute management of ST-segment elevation myocardial infarction are appropriately matched to their mechanism of effect EXCEPT:

- A. Aspirin – reduction in thromboxane A_2
- B. Abciximab – inhibition of the glycoprotein IIb/IIIa receptor
- C. β -Adrenergic antagonists – reduced myocardial oxygen consumption
- D. Clopidogrel – inhibition of the platelet adenosine diphosphate (ADP) receptor
- E. Nitroglycerin – reduced cardiac afterload

134. A 61-year-old man presented to the emergency department 2 hours ago with anginal chest pain and ST-segment elevations in I, aVL, and V_1 – V_3 . At the time, the interventional cardiologist on call was involved in a complex case and was unable to take the patient for prompt primary percutaneous coronary intervention; thus tissue plasminogen activator (tPA) was administered. However, 120 minutes after administration of tPA, the patient continues to complain of chest pain, and his ECG shows no resolution of ST-segment elevations. What is the next most appropriate step?

- A. Administer a second dose of tPA
- B. Administer streptokinase 1.5 million units over 1 hour
- C. Proceed with urgent coronary artery bypass grafting
- D. Proceed with urgent percutaneous coronary intervention
- E. Wait for 60 more minutes before pursuing any other therapeutic options

135. Mr. Cooper underwent tPA administration for acute ST-segment elevation myocardial infarction 1 hour previously.

He had an excellent response with resolution of his ST-segment elevation and chest pain. However, the nurse pages you to evaluate a change in his rhythm. You note a wide complex ventricular rhythm with a rate of 75 bpm. Mr. Cooper continues to feel well without new symptoms and his blood pressure is 120/80 mmHg. The next most appropriate therapeutic maneuver is which of the following?

- A. Administer amiodarone 150 mg IV over 10 minutes
- B. Administer flecainide 400 mg orally
- C. Administer metoprolol 5 mg IV every 5 minutes $\times$ 3
- D. Carotid sinus massage
- E. Continue observation

136. An 84-year-old woman with a history of diabetes and hyperlipidemia presented to the emergency department 3 weeks ago with an ST-segment elevation myocardial infarction. She underwent emergent primary percutaneous coronary intervention to an acutely occluded left anterior descending artery. A 3.5×24 mm² everolimus-eluting stent was placed with excellent angiographic result and complete resolution of her symptoms. She has been feeling excellent since then. Her discharge medications were metoprolol, aspirin, clopidogrel, rosuvastatin, lisinopril, and sliding scale insulin. She recently went to see her ophthalmologist who noted a right eye cataract. The ophthalmologist has contacted your office asking about your opinion on discontinuing her aspirin and/or clopidogrel to reduce bleeding risk during her cataract surgery, which has been scheduled for next week. She feels the bleeding risk on both medications is too high to perform the surgery. Which of the following should you recommend?

- A. “Discontinue aspirin, continue clopidogrel, and proceed with cataract surgery.”
- B. “Discontinue clopidogrel, continue aspirin, and proceed with cataract surgery.”
- C. “Discontinue both aspirin and clopidogrel and proceed with cataract surgery.”
- D. “Postpone the surgery for at least 6 months, and preferably 12 months, at which time the clopidogrel can be discontinued.”
- E. “I advise to perform the surgery while she is on both aspirin and clopidogrel as she will never be able to stop either medication.”

137. Ms. Constance is a 65-year-old recently retired librarian with a history of hypertension. After retirement, she began an exercise walking program but noted that she was markedly short of breath and had moderate chest pressure after only two to three blocks. She presented to your office 2 weeks ago. Given your concern that her symptoms were due to coronary artery disease, you referred her to a cardiologist for diagnostic coronary angiography. That was performed 1 week ago and revealed high-grade focal stenoses of the proximal left anterior descending artery, left circumflex artery, and right coronary artery. Other than these lesions,

she did not have flow-limiting disease. The cardiologist did not perform percutaneous coronary intervention (PCI) and recommended a conversation with the local cardiothoracic surgeon to consider coronary artery bypass grafting (CABG). Ms. Constance now returns to your clinic for advice. You have the cardiologist and the cardiothoracic surgeon on conference call during the meeting. When counseling Ms. Constance about which revascularization strategy to choose, which of the following statements is true?

- A. CABG has a lower mortality rate at 1 year than PCI for patients like Ms. Constance.
- B. At 1 year, patients like Ms. Constance undergoing CABG have a higher risk of needing other procedures for revascularization than patients undergoing PCI.
- C. PCI carries a higher risk of stroke than CABG.
- D. The characteristics of coronary anatomy and the cardiologist's anticipation of success with PCI should factor into the decision.
- E. PCI has a lower rate of myocardial infarction at 1 year than CABG for patients like Ms. Constance.

138. Mr. Gruentzig presents to your cardiology practice for shortness of breath and mild chest pressure with exertion. After a careful history and physical examination and a thorough discussion with the patient of the risks and benefits, you refer him for a technetium-99m scan, which reveals infero-apico-posterior ischemia. You promptly refer him to your colleague for coronary angiography. At angiography, he is found to have a left dominant system with a totally occluded left circumflex artery. The distal left circumflex artery is filled via collaterals from the left anterior descending artery. The interventional cardiologist is quite skilled, but she is unable to cross the total occlusion in the left circumflex using a hydrophilic wire and the antegrade approach. Which of the following statements regarding intervention on this chronic total occlusion (CTO) is true?

- A. If the CTO cannot be crossed with any wire in the antegrade approach, the operator should always abandon percutaneous repair and consider referral for coronary bypass surgery.
- B. Attempting to access the CTO via a retrograde approach through a collateral vessel is an option when attempting percutaneous revascularization.
- C. Although the presence of a CTO is associated with a higher mortality rate, successful PCI of a CTO has never been shown to lower this mortality rate.
- D. Coronary artery bypass surgery of a CTO is rarely successful due to the atretic nature of the vessel distal to the chronically occluded segment.
- E. In studies, successful revascularization of chronic total coronary occlusions is associated with symptom relief but no improvement in left ventricular function.

139. A 67-year-old former truck driver underwent four-vessel CABG 12 years earlier with a left internal mammary artery (LIMA) graft to the left anterior descending artery (LAD),

and three saphenous vein grafts (SVGs) to the first diagonal, first obtuse marginal, and right posterior descending arteries. At your visit with him today, he reports approximately 1 month of accelerating chest pain and shortness of breath with decreasing amounts of exertion. You refer him for coronary angiography, which reveals significant stenosis in the body of the SVG to the first obtuse marginal branch. Which of the following statements are true?

- A. Graft failure of an SVG is almost always from thrombus embolized from the aortic anastomosis site.
- B. PCI to this saphenous vein graft will require deployment of a distal protective device.
- C. PCI on a saphenous vein graft is too risky to warrant proceeding. Aggressive medical management with antianginal therapy should be pursued.
- D. The risk of PCI to an SVG is identical to native-vessel PCI.
- E. Venous and arterial graft conduits (e.g., SVG and LIMA grafts) have identical patency rate over the first 5 years following bypass grafting.

140. Mrs. Edwards is an 87-year-old woman with a history of extensive tobacco abuse and resultant COPD with a forced expiratory volume in 1 second (FEV₁) of 0.76 L, poorly controlled diabetes, and stage III chronic kidney disease. She was previously your patient but has not followed up with you for the preceding 8 years. However, she comes to your clinic today complaining of chest pressure with exertion, leg swelling, shortness of breath, and accelerating fatigue with even minimal exertion. On examination, you quickly note a harsh, late-peaking systolic murmur at the right upper sternal border radiating the carotid arteries and with a musical quality at the apex. You cannot appreciate a second heart sound, and the carotid impulses are muted and arrive late compared to the PMI on palpation. You suspect severe aortic stenosis, and indeed, an echocardiogram later that day confirms aortic stenosis with a valve area of 0.59 cm². You refer Mrs. Edwards to a cardiothoracic surgeon who informs you that Mrs. Edwards is much too high risk for a surgical aortic valve replacement, citing a higher than 15% risk of in-hospital mortality. You are due to see Mrs. Edwards tomorrow. Which of the following statements to her would be reasonable?

- A. "For this condition, medications have been shown to reduce the risk of mortality."
- B. "It is okay that you are not a surgical candidate. Your condition carries a low risk of 1- and 5-year mortality, and we can control your symptoms with medications."
- C. "Percutaneous aortic balloon valvotomy is a good nonsurgical treatment option and has been found to have excellent short- and long-term outcomes."
- D. "Since you are not a surgical candidate, no other procedure exists for aortic valve replacement for you. We should consider hospice options."
- E. "We should consider referring you for further testing to see if you are a candidate for transcatheter aortic valve replacement."

- 141.** All of the following statements regarding the epidemiology of hypertension are true EXCEPT:
- Among individuals age 60 years or older, average systolic blood pressure is higher in women.
 - Diastolic blood pressure increases steadily with age throughout life.
 - Hypertension prevalence is lower in Mexican Americans than non-Hispanic whites.
 - In industrialized nations, blood pressure increases steadily during the first two decades of life.
 - In the United States, approximately 30% of adults have hypertension.
- 142.** Disease of which organ is the most common cause of mortality in hypertensive patients?
- Brain
 - Heart
 - Kidney
 - Liver
 - Lungs
- 143.** A 28-year-old woman has hypertension that is difficult to control. She was diagnosed at age 26. Since that time, she has been on increasing amounts of medication. Her current regimen consists of labetalol 1000 mg twice a day (bid), lisinopril 40 mg once a day (qd), clonidine 0.1 mg bid, and amlodipine 5 mg qd. On physical examination, she appears to be without distress. Blood pressure is 168/100 mmHg and heart rate is 84 bpm. Cardiac examination is unremarkable, without rubs, gallops, or murmurs. She has good peripheral pulses and no edema. Her physical appearance does not reveal any hirsutism, fat maldistribution, or abnormalities of genitalia. Laboratory studies reveal a potassium of 2.8 mEq/dL and a serum bicarbonate of 32 mEq/dL. Fasting blood glucose is 114 mg/dL. What is the most likely diagnosis?
- Congenital adrenal hyperplasia
 - Fibromuscular dysplasia
 - Cushing syndrome
 - Conn syndrome
 - Pheochromocytoma
- 144.** What is the best way to diagnose the disease in the patient described in Question 143?
- Renal vein renin levels
 - 24-hour urine collection for metanephrines
 - MRI of the renal arteries
 - 24-hour urine collection for cortisol
 - Plasma aldosterone/renin ratio
- 145.** Mr. Wilkins is a 65-year-old aeronautics engineer who has never been to the doctor and takes no medications. He is brought to the emergency department by his wife for worsening headache over the last day and confusion starting about an hour ago. His blood pressure on presentation is 230/140 mmHg and heart rate is 90 bpm. Arterial oxygen saturation is 95%. On examination, he is moving all extremities equally, and there are no obvious deficits in his cranial nerve function, but he is clearly delirious. Cardiac examination reveals an enlarged and forceful PMI and an S₄ gallop; his lungs are clear to auscultation. Laboratory studies show a creatinine of 2.4 mg/dL, 2+ protein in his urine with hematuria, and a hematocrit of 32% with normal platelet count. You examine his peripheral blood smear and notice schistocytes. Emergent brain MRI shows old microvascular changes but no acute infarct or hemorrhage. Regarding his blood pressure management, which of the following would be the most reasonable therapeutic course?
- 0.1 mg of clonidine orally
 - 20 mg of oral lisinopril
 - 20 mg of IV labetalol and initiation of a continuous parenteral drip for goal mean arterial pressure of 125 mmHg in the first hour
 - 90 mg of immediate-release oral nifedipine
 - Emergent plasmapheresis
- 146.** Which of the following statements regarding the physiology of renal perfusion is true?
- Due to tight precapillary regulation, the glomerular capillary endothelium is relatively shielded from pressure injury.
 - Renal cortical blood flow is less than renal medullary blood flow and coupled with the high metabolic needs of the renal cortex, this leaves that region bordering on hypoxemia.
 - Renal perfusion is tightly regulated to the metabolic needs of the kidney.
 - Urinary albumin excretion is predictive of systemic atherosclerotic events and can present years in advance of clinical atherosclerotic disease.
 - Venous blood returning from the renal cortex has a lower oxygen content than venous blood returning from the renal medulla.
- 147.** Which of the following statements regarding renal artery stenosis is true?
- An abnormally reduced renal artery flow velocity by Doppler ultrasound is predictive of hemodynamically significant stenosis.
 - Early in the course of renal artery stenosis, elevated systemic renin levels are typical.
 - In the general population, the presence of fibromuscular dysplasia is rare (<1% prevalence).
 - Levels of renin activity observed in renal artery stenosis are predictive of response to medical therapy.
 - Usually the first clinical presentation of renal stenosis due to fibromuscular dysplasia is reduced renal function.

- 148.** A 75-year-old man underwent a diagnostic coronary angiography after an abnormal stress test. Arterial access was obtained easily in the right femoral artery and the angiography was completed with 35 mL of iodinated contrast dye. Fortunately, no significant coronary stenoses were noted. Seven days later, the man presents to the emergency department with abdominal pain and nausea. He reports that his urine output has been poor recently. Examination reveals a slight fever (38.3°C) and livedo reticularis on his lower extremities. Laboratory studies show a creatinine of 2.7 mg/dL (previously 1.1 mg/dL), white blood cell count of 10,500/mL with 21% eosinophils, and an erythrocyte sedimentation rate of 92 mm/h. What is the mostly likely diagnosis?
- Acute interstitial nephritis
 - Atheroembolic renal disease
 - Churg-Strauss syndrome
 - Contrast-induced nephropathy
 - Hypereosinophilic syndrome
- 149.** In which of the following patients who present to an emergency department reporting acute dyspnea would a positive D-dimer result prompt additional testing for a pulmonary embolus?
- A 24-year-old woman who is 32 weeks pregnant
 - A 48-year-old man with no past medical history who presents with calf pain following prolonged air travel; alveolar-arterial oxygen gradient is normal
 - A 56-year-old woman undergoing chemotherapy for breast cancer
 - A 62-year-old man who underwent hip replacement surgery 4 weeks previously
 - A 72-year-old man who had an acute myocardial infarction 2 weeks ago
- 150.** A 42-year-old woman presents to the emergency department with acute onset of shortness of breath. She recently had been to visit her parents out of state and rode in a car for about 9 hours each way. Two days ago, she developed mild calf pain and swelling, but she thought that this was not unusual after having been sitting with her legs dependent for the recent trip. On arrival to the emergency department, she is noted to be tachypneic. Her vital signs are blood pressure 98/60 mmHg, heart rate 114 bpm, respiratory rate 28 bpm, oxygen saturation 92% on room air, and weight 89 kg. The lungs are clear bilaterally. There is pain in the right calf with dorsiflexion of the foot and the right leg is more swollen when compared to the left. An arterial blood gas measurement shows a pH of 7.52, PCO₂ of 25 mmHg, and PO₂ of 68 mmHg. Kidney and liver functions are normal. A helical CT scan confirms a pulmonary embolus. All of the following agents can be used alone as initial therapy in this patient EXCEPT:
- Enoxaparin 1 mg/kg subcutaneously (SC) twice daily
 - Fondaparinux 7.5 mg SC once daily
 - Tinzaparin 175 units/kg SC once daily
 - Unfractionated heparin IV adjusted to maintain activated partial thromboplastin time (aPTT) two to three times the upper limit of normal
 - Warfarin 7.5 mg orally once daily to maintain international normalized ratio at 2–3
- 151.** Which of the following statements regarding pulmonary embolism is true?
- Airway resistance usually decreases in the setting of an acute pulmonary embolism.
 - Almost all patients with pulmonary embolism have evidence of deep vein thrombosis at the time.
 - Alveolar hyperventilation is a typical physiologic abnormality in the presence of pulmonary embolism.
 - Hypotension in the setting of acute pulmonary embolism is often due to acute left ventricular systolic dysfunction.
 - The size of the arterial-alveolar gradient is invariably correlated with the size of the pulmonary embolism.
- 152.** A 57-year-old man with a history of hypertension is admitted to the hospital with pulmonary embolism after having sudden onset of chest discomfort. His blood pressure is 132/62 mmHg, heart rate is 85 bpm, and oxygen saturation is 95% on room air. Echocardiography reveals normal right heart size and function, and cardiac troponin I is undetectable. Lower extremity Doppler ultrasound reveals an extensive deep vein thrombus from the right femoral popliteal vein. The patient is started on low-molecular-weight heparin and concomitant warfarin. On rounds the following day, he asks if insertion of an inferior vena cava (IVC) filter would be appropriate. What is the most appropriate answer?
- “No, you would not benefit from an IVC filter at this point.”
 - “No, there are currently no indications for IVC filter placement in the setting of deep vein thrombus or pulmonary embolism.”
 - “We will need to go back to review your images and see how large your pulmonary embolus clot burden is before deciding whether an IVC filter is appropriate for you or not.”
 - “Yes, given the presence of residual lower extremity thrombus, we will schedule you for IVC filter insertion.”
 - “Yes, given your age and gender, we will schedule you for an IVC filter insertion.”
- 153.** Mrs. Tupulo is a 45-year-old woman with a history of morbid obesity (weight 140 kg), hypertension, and diabetes. She

has been in the hospital for 4 days after having open surgical gastric bypass surgery. On postoperative day 4, she experiences sudden breathlessness, tachycardia, hypoxia, and an overwhelming sense of impending doom. Urgent chest CT angiography reveals a saddle pulmonary embolism. Her blood pressure is 70/45 mmHg and urine output is poor. Five hundred milliliters of normal saline are administered IV and she is initiated on dobutamine 5 µg/kg/min with a subsequent blood pressure of 82/55 mmHg. What is the next most appropriate step?

- A. Enoxaparin
- B. IVC filter
- C. Surgical pulmonary embolectomy
- D. tPA
- E. Urokinase

154. A 67-year-old former heavy smoker is postoperative day 4 from an open aortobifemoral bypass operation for severe claudication. On routine postoperative CT scan prior to discharge, a pseudoaneurysm is noted just proximal to the aortic origin of the bypass grafts. Which of the following best defines a pseudoaneurysm?

- A. A focal dilation in a vessel in which the intimal and medial layers are disrupted and the dilated segment is lined by adventitia only
- B. A focal dilation of a vessel only involving one portion of the circumference
- C. Apparent dilation of a vessel due to intrinsic narrowing proximal and distal to the point of apparent narrowing
- D. Dilation of a vessel, though not to the size necessary to be diagnosed as a true aneurysm
- E. The appearance of an aneurysmal dilation of a vessel on imaging due to the angulation of the artery and imaging technique

155. All of the following factors are associated with elevated risk for the development of an aortic aneurysm EXCEPT:

- A. Aging
- B. Cigarette smoking
- C. Female sex
- D. Hypercholesterolemia
- E. Hypertension

156. You are seeing Mr. Walker in clinic for follow-up. He is a 22-year-old man with a family history of sudden death and arterial aneurysms. He is quite tall with widely spaced eyes and a bifid uvula. On his first visit, you order a transthoracic echocardiogram to investigate a diastolic murmur and note an aortic root aneurysm of 4.9 cm. He most likely has a mutation in which of the following genes?

- A. Fibrillin-1
- B. SMAD3
- C. Smooth muscle-specific α -actinin
- D. TGF- β receptor
- E. Type III procollagen

157. Which of the following patients with aortic dissection or hematoma is best managed without surgical therapy?

- A. A 45-year-old female with a dissection involving the aorta distal to the great vessel origin but cephalad to the renal arteries.
- B. A 74-year-old male with a dissection involving the root of the aorta.
- C. A 58-year-old male with aortic dissection involving the distal aorta and the bilateral renal arteries.
- D. A 69-year-old male with an intramural hematoma within the aortic root.
- E. All of the above patients require surgical management of their aortic disease.

158. A 32-year-old woman is seen in the emergency department for acute shortness of breath. A helical CT shows no evidence of pulmonary embolus, but incidental note is made of dilatation of the ascending aorta to 4.3 cm. All the following are associated with this finding EXCEPT:

- A. Giant cell arteritis
- B. Rheumatoid arthritis
- C. Syphilis
- D. Systemic lupus erythematosus
- E. Takayasu arteritis

159. Mr. Tomazelli is a 75-year-old man with diabetes mellitus and hypertension. Despite continued counseling, he has been unable to stop smoking imported unfiltered cigarettes. At your visit today, he complains of burning pain in his bilateral calves with ambulation. It typically occurs after about two city blocks of walking on flat ground and improves with rest. He has also noted some aching calf pain during the night that improves when he sits on the side of the bed. Which of the following is likely true for Mr. Tomazelli?

- A. He likely has critical aorto-iliac arterial stenosis.
- B. The amplitude of his pulse volume contour will be sharp and spiked.
- C. The most likely etiology of his symptoms is femoral arterial fibromuscular dysplasia.
- D. The next most reasonable diagnostic test is magnetic resonance angiography.
- E. The ratio of the systolic blood pressure in his ankle versus his brachial artery is likely less than 0.9.

160. The patient described in Question 159 is diagnosed with symptomatic peripheral arterial disease (PAD) with bilateral ankle-brachial indices of 0.82. He asks about his prognosis and what the next step in treatment should be. Which of the following statements regarding his prognosis and therapy is true?

- A. Anticoagulation with warfarin is superior to antiplatelet agents in preventing adverse cardiovascular events in patients with PAD.
- B. β -Adrenergic blockers have been shown to worsen limb ischemia and should not be used in PAD.
- C. He should exercise daily, walking to the point of maximal claudication before stopping to rest and allowing his symptoms to resolve.
- D. His greatest risk of morbidity and mortality over the ensuing 5 years is progression to critical limb ischemia.
- E. Vasodilators are first-line therapy for symptomatic PAD.

161. A 37-year-old woman with no significant past medical history except for a childhood murmur is evaluated for sudden-onset severe pain in her right lower extremity. Examination is notable for a young, uncomfortable woman with normal vital signs except for a heart rate of 110 bpm. The right leg has pallor distal to the right knee and is cold to the touch, and the dorsalis pedis pulse is absent. The left leg is normal. Which of the following studies is likely to diagnose the underlying reason for the patient's presentation?

- A. Angiography of right lower extremity
- B. Blood cultures
- C. Echocardiogram with bubble study
- D. Serum cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA)
- E. Venous ultrasound of right upper extremity

162. A 32-year-old construction foreman presents with exertional pain in his bilateral forearms and hands. He smokes one pack of cigarettes per day, but otherwise has no past medical history. He has an easily palpable brachial pulse but very faint radial and ulnar pulses. A picture of his hand is shown in Figure 24. Angiography of his upper extremity reveals smooth tapering segmental lesions in the small distal arterial vessels. Which of the following treatments has the greatest chance of success?

- A. Cilostazol
- B. Enoxaparin
- C. Prednisone
- D. Smoking cessation
- E. Warfarin

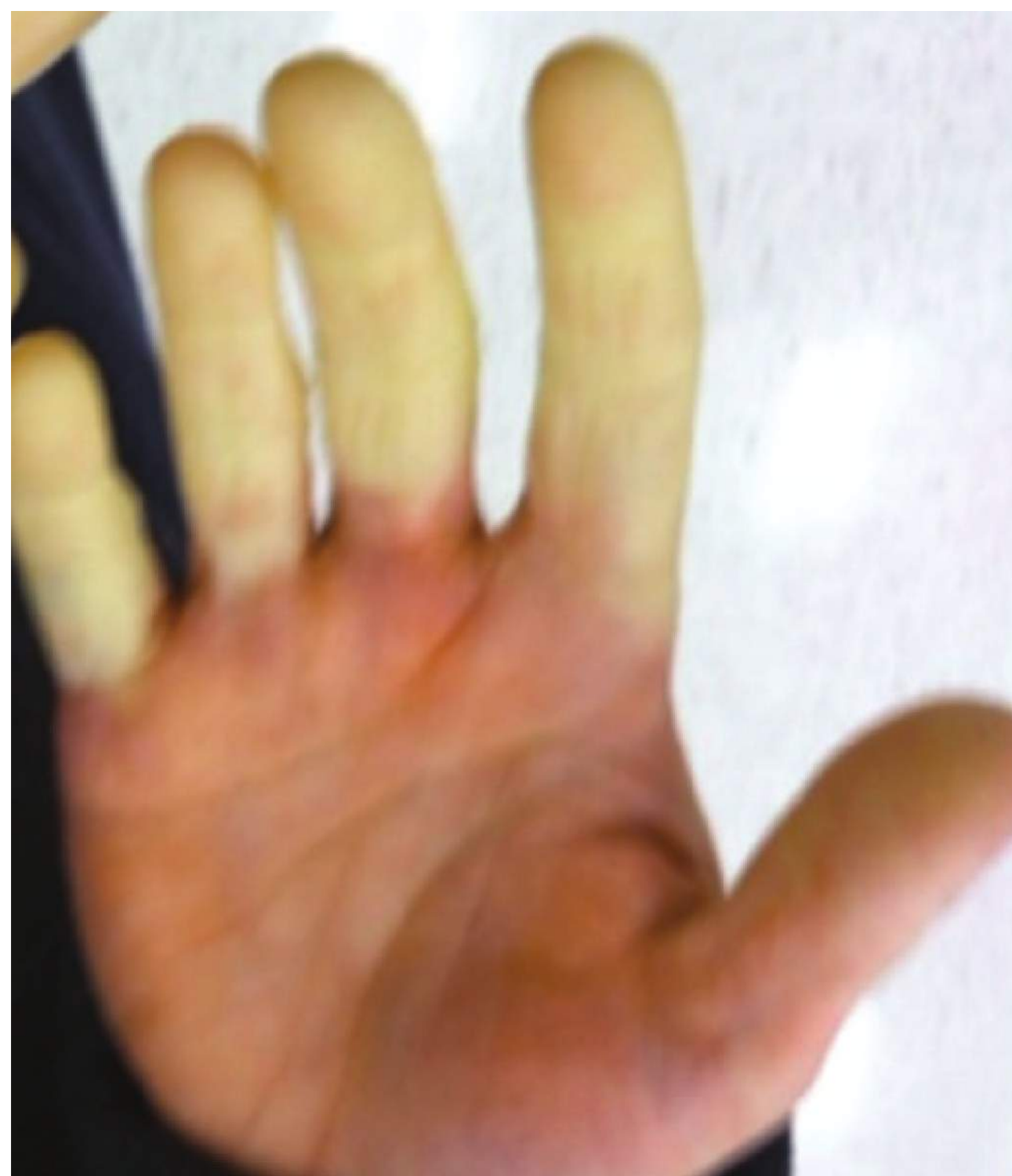


FIGURE 24

163. Which of the following statements regarding chronic venous disease is true?

- A. More men than women suffer from varicose veins.
- B. More men than women suffer from chronic venous insufficiency with edema.
- C. More than 50% of patients over 70 years old have chronic venous insufficiency.
- D. Most patients with chronic venous insufficiency will develop venous ulcers.
- E. All of the above are true.

164. Which of the following is the longest vein in the body?

- A. Azygous vein
- B. Greater saphenous vein
- C. Inferior vena cava
- D. Left common iliac vein
- E. Right common femoral vein

165. You are evaluating a 77-year-old woman from Ohio with a history of heart failure with preserved ejection fraction, diabetes mellitus, and prior left lower extremity deep venous thrombosis status post a course of anticoagulation. For the past several months, she has complained of a cramping, burning sensation in her legs. Today she presents for evaluation of a skin ulcer, shown in Figure 25. On examination, you note the skin ulceration over the medial malleolus and a nonpitting woody-type edema of the bilateral ankles and shins. The skin there is darker as well. The ulcer is most likely due to which of the following?

- A. Arachnid envenomation
- B. Bacillus anthracis infection
- C. Chronic venous insufficiency
- D. Diabetic foot ulcer
- E. Peripheral arterial disease



FIGURE 25 Courtesy of Dr. Steven Dean, with permission.

166. You are evaluating a 19-year-old woman in a travel clinic at your university. She complains of a nonpainful swelling of the lower extremity. On examination, the leg has thickened skin and a woody texture. A bedside ultrasound confirms patent lower extremity veins without thrombus. You suspect lymphedema and think that this is likely due to the most common cause of secondary lymphedema worldwide. What cause do you suspect?

- A. Cancer involving the inguinal lymph nodes
- B. Lymphogranuloma venereum
- C. Lymphatic filariasis
- D. Recurrent bacterial lymphangitis
- E. Tuberculosis

167. You are taking care of a patient who suffers from chronic lymphedema due to recurrent streptococcal lymphangitis as a child. She finds her leg swelling unsightly and asks about therapeutic options. All of the following are reasonable therapeutic options for chronic lymphedema EXCEPT:

- A. Decongestive physiotherapy
- B. Diuretic therapy
- C. Frequent leg elevation
- D. Intermittent pneumatic compression devices
- E. Liposuction

ANSWERS

1. The answer is C.

(Chap. 2) The global rise in cardiovascular disease (CVD) is the result of an unprecedented transformation in the causes of morbidity and mortality during the 20th century. Known as the epidemiologic transition, this shift is driven by industrialization, urbanization, and associated lifestyle changes and is taking place in every part of the world among all races, ethnic groups, and cultures. The transition is divided into four basic stages: pestilence and famine, receding pandemics, degenerative and man-made diseases, and delayed degenerative diseases. A fifth stage, characterized by an epidemic of inactivity and obesity, is emerging in some countries. The stages of the epidemiologic transition are shown in Table 1.

Note that CVD mortality peaks in the third stage and then tends to decline aided by preventive strategies such as smoking cessation programs and effective blood pressure control, acute hospital management, and technologic advances, such as the availability of bypass surgery. In the stage of receding pandemics, the majority of CVD risk tends to be due to coronary heart disease, stroke, and rheumatic heart disease. Although the stages of epidemiologic transition is a useful construct to generalize expectations regarding CVD epidemiology over time, every nation experiences these stages in unique fashion due to environmental, behavioral, and genetic differences. For example, in China and Japan, stroke causes more deaths than coronary heart disease in a ratio of about 3:1, as we would expect for this hypothetical nation.

TABLE 1 Five Stages of the Epidemiologic Transition

Stage	Description	Deaths Related to CVD, %	Predominant CVD Type
Pestilence and famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths related to malnutrition and infection; precipitous decline in infant and child mortality rates	10–35	Rheumatic valvular disease, hypertension, CHD, and stroke (predominantly hemorrhagic)
Degenerative and man-made diseases	Increased fat and caloric intake and decrease in physical activity lead to emergence of hypertension and atherosclerosis; with increase in life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious disease	35–65	CHD and stroke (ischemic and hemorrhagic)
Delayed degenerative diseases	CVD and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events; age-adjusted CVD mortality declines; CVD affecting older and older individuals	40–50	CHD, stroke, and congestive heart failure
Inactivity and obesity	Overweight and obesity increase at alarming rate; diabetes and hypertension increase; decline in smoking rates levels off; a minority of the population meets physical activity recommendations	33	CHD, stroke, and congestive heart failure, peripheral vascular disease

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.
Source: Adapted from AR Omran: The epidemiologic transition: A theory of the epidemiology of population change. *Milbank Mem Fund Q* 49:509, 1971; and SJ Olshansky, AB Ault: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. *Milbank Q* 64:355, 1986.

2. The answer is C.

(Chap. 9) This patient has classic findings of differential cyanosis, or isolated cyanosis (and clubbing in this case) of the lower, but not upper, extremities. This limits the differential diagnosis to only one possibility: patent ductus arteriosus with secondary pulmonary hypertension causing right-to-left shunting at the level of the great vessels, distal

to the upper extremity branches. Tetralogy of Fallot often causes central cyanosis due to right-to-left intracardiac shunting with no differential between the upper and lower extremities. Ventricular septal defect (VSD) and atrial septal defect (ASD) often have no cyanosis evident as they are most often left-to-right shunts (unless pulmonary hypertension develops resulting in Eisenmenger syndrome).

Transposition of the great arteries (TGA) may exhibit varying degrees of central cyanosis, depending on the intracardiac anatomy (most often present with an ASD).

3. The answer is C.

(Chap. 9) The electrocardiogram (ECG) shows complete heart block, and the leg lesions are consistent with erythema nodosum. This combination of findings is most likely due to sarcoidosis. Extrapulmonary sarcoidosis may manifest as cardiac conduction abnormalities (most common at the atrioventricular [AV] node), skin and joint lesions, hypercalcemia, and neurologic deficits. Hypothyroidism may cause sinus bradycardia but is usually not a cause of complete heart block. Also, the lower extremity skin finding of hypothyroidism is myxedema, a doughy, nonpitting, nonpainful edema. Carney syndrome is characterized by multiple lentigines and atrial myxomata. Systemic lupus erythematosus can be associated by erythema nodosum, although it does not often cause conduction system disease in adults. However, neonatal lupus is a common cause of complete heart block.

4. The answer is E.

(Chap. 9) Jugular venous pulse (JVP) is the single most important physical examination measurement from which to estimate a patient's volume status. The internal jugular vein is preferred because the external jugular vein is valved and not directly in line with the superior vena cava and right atrium. Precise estimation of the central venous or right atrial pressure from bedside assessment of the jugular venous waveform has proved difficult. Venous pressure traditionally has been measured as the vertical distance between the top of the jugular venous pulsation and the sternal inflection point (angle of Louis). A distance >4.5 cm at 30 degrees of elevation is considered abnormal. However, the actual distance between the mid-right atrium and the angle of Louis varies considerably as a function of both body size and the patient angle at which the assessment is made (30, 45, or 60 degrees). The use of the sternal angle as a reference point leads to systematic underestimation of central venous pressure (CVP), and this method should be used less for semi-quantification than to distinguish a normal from an abnormally elevated CVP. Venous pulsations above the right clavicle in the sitting position are clearly abnormal, as the distance between the clavicle and the right atrium is at least 10 cm. Normally, the venous pressure should fall by at least 3 mmHg with inspiration. Kussmaul sign is defined by either a rise or a lack of fall of the JVP with inspiration and is classically associated with constrictive pericarditis, although it has been reported in patients with restrictive cardiomyopathy, massive pulmonary embolism, right ventricular infarction, and advanced left ventricular systolic heart failure. It is also a common, isolated finding in patients after cardiac surgery without other hemodynamic abnormalities.

5. The answer is A.

(Chap. 9) The length and width of the blood pressure cuff bladder should be 80% and 40% of the arm's circumference, respectively. A common source of error in practice is to use an inappropriately small cuff, resulting in marked overestimation of true blood pressure, or an inappropriately large cuff, resulting in underestimation of true blood pressure. The cuff should be inflated to 30 mmHg above the expected systolic pressure and the pressure released at a rate of 2–3 mmHg/s. Systolic and diastolic pressures are defined by the first and fifth Korotkoff sounds, respectively. Very low (even 0 mmHg) diastolic blood pressures may be recorded in patients with chronic, severe aortic regurgitation (AR) or a large arteriovenous fistula because of enhanced diastolic "run-off." In these instances, both the phase IV and phase V Korotkoff sounds should be recorded. Blood pressure is best assessed at the brachial artery level, although it can be measured at the radial, popliteal, or pedal pulse level. In general, measured systolic pressure increases and diastolic pressure decreases when measured in more distal arteries. Blood pressure should be measured in both arms, and the difference should be less than 10 mmHg. A blood pressure differential that exceeds this threshold may be associated with atherosclerotic or inflammatory subclavian artery disease, supraaortic stenosis, aortic coarctation, or aortic dissection. Systolic leg pressures are usually as much as 20 mmHg higher than systolic arm pressures. Greater leg–arm pressure differences are seen in patients with chronic severe AR as well as patients with extensive and calcified lower extremity peripheral arterial disease. The ankle-brachial index (lower pressure in the dorsalis pedis or posterior tibial artery divided by the higher of the two brachial artery pressures) is a powerful predictor of long-term cardiovascular mortality. The blood pressure measured in an office or hospital setting may not accurately reflect the pressure in other venues. "White coat hypertension" is defined by at least three separate clinic-based measurements $>140/90$ mmHg and at least two non-clinic-based measurements $<140/90$ mmHg in the absence of any evidence of target organ damage. Individuals with white coat hypertension may not benefit from drug therapy.

6. The answer is E.

(Chap. 9) This patient has evidence of pulsus alternans. Pulsus alternans is defined by beat-to-beat variability of pulse amplitude. It is present only when every other phase I Korotkoff sound is audible as the cuff pressure is lowered slowly, typically in a patient with a regular heart rhythm and independent of the respiratory cycle. Pulsus alternans is seen in patients with severe left ventricular systolic dysfunction and is thought to be due to cyclic changes in intracellular calcium and action potential duration. When pulsus alternans is associated with electrocardiographic T-wave alternans, the risk for an arrhythmic event appears to be increased. Cardiac tamponade or large pericardial effusions can be associated with electrical alternans (a regular

variability in the QRS voltage or vector) or pulsus paradoxus, a difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each heartbeat, independent of the respiratory phase. T is an exaggerated consequence of interventricular dependence. Atrial fibrillation would result in beat-to-beat variability of the pulse amplitude but also an irregularly irregular rhythm.

7. T e answer is A.

(Chap. 9) A fourth heart sound indicated left ventricular presystolic expansion and is common among patients in whom active atrial contraction is important for ventricular filling. A fourth heart sound is not found in atrial fibrillation. An irregular heart rate is characteristic of atrial fibrillation. T e irregular rate is often characterized as “irregularly irregular.” A third heart sound occurs during the rapid filling phase of ventricular diastole and indicates heart failure. Reversed splitting of the second heart sound occurs with left bundle branch block, as this patient demonstrates. Kussmaul sign is defined by either a rise or a lack of fall of the JVP with inspiration and is classically associated with constrictive pericarditis, although it has been reported in patients with restrictive cardiomyopathy, massive pulmonary embolism, right ventricular infarction, and advanced left ventricular systolic heart failure. It is also a common, isolated finding in patients after cardiac surgery without other hemodynamic abnormalities.

8. T e answer is F.

(Chap. 9) When a murmur of uncertain cause is identified on physical examination, a variety of physiologic maneuvers can be used to assist in the elucidation of the cause. Commonly used physiologic maneuvers include change with respiration, Valsalva maneuver, position, and exercise. In hypertrophic cardiomyopathy, there is asymmetric hypertrophy of the interventricular septum, which creates a dynamic outflow obstruction. Maneuvers that decrease left ventricular filling will cause an increase in the intensity of the murmur, whereas those that increase left ventricular filling will cause a decrease in the murmur. Of the interventions listed, both standing and a Valsalva maneuver will decrease venous return and subsequently decrease left ventricular filling, resulting in an increase in the loudness of the murmur of hypertrophic cardiomyopathy. Alternatively, squatting increases venous return and thus decreases the murmur. Maximum handgrip exercise also results in a decreased loudness of the murmur.

9. T e answer is A.

(Chap. 9) T e patient is likely to have pericardial tamponade from metastatic cancer as suggested by her elevated neck veins, heart shadow shape and size, and predisposing condition. Because of the exaggerated interventricular dependence, the normal (<10 mmHg) fall in systemic

blood pressure with inspiration is exaggerated (often >15 mmHg) with cardiac tamponade. T is referred to pulsus paradoxus, although it is in fact an augmentation of a normal finding. Kussmaul sign, or a lack of fall of the jugular venous pressure with inspiration, is a sign usually denoting a lack of compliance in the right ventricle, as seen most frequently in constrictive pericarditis, although it may be found in restrictive cardiomyopathy or massive pulmonary embolism. A slow y-descent, which follows the peak of the v wave, of jugular venous pressure tracing is indicative of cardiac tamponade as the restricted ventricle is slow to fill during diastole. T e x-descent (systolic) may be augmented because ventricular ejection results in relative unloading of the intrapericardial pressure. Pulsus parvus et tardus, or small and slow arterial pulsation, is a late finding in aortic stenosis. Late diastolic murmur with opening snap is found in mitral stenosis.

10. T e answer is B.

(Chap. 11) T e depolarization stimulus for the normal heartbeat originates in the sinoatrial (SA) node, or sinus node, a collection of pacemaker cells. T ese cells fire spontaneously; that is, they exhibit automaticity. Other cells exhibit automaticity, although at a slower rate, including AV nodal (junctional) cells and the Purkinje fiber cells. T e first phase of cardiac electrical activation is the spread of the depolarization wave through the right and left atria, followed by atrial contraction. Next, the impulse stimulates pacemaker and specialized conduction tissues in the AV nodal and His bundle areas; together, these two regions constitute the AV junction. T e bundle of His bifurcates into two main branches, the right and left bundles, which rapidly transmit depolarization wavefronts to the right and left ventricular myocardium by way of Purkinje fibers. T e main left bundle bifurcates into two primary subdivisions: a left anterior fascicle and a left posterior fascicle. T e depolarization wavefronts then spread through the ventricular wall, from endocardium to epicardium, triggering ventricular contraction.

11. T e answer is A.

(Chap. 11) T e ECG waveforms are labeled alphabetically, beginning with the P wave, which represents atrial depolarization. T e QRS complex represents ventricular depolarization, and the ST-T-U complex (ST segment, T wave, and U wave) represents ventricular repolarization. T e J point is the junction between the end of the QRS complex and the beginning of the ST segment. Atrial repolarization (STa and Ta) is usually too low in amplitude to be detected, but it may become apparent in conditions such as acute pericarditis and atrial infarction.

12. T e answer is A.

(Chap. 11) Figure 26 depicts the limb leads and respective frontal plane axis categories on the ECG. Note that normal axis extends from -30 to 90 or 100 degrees.

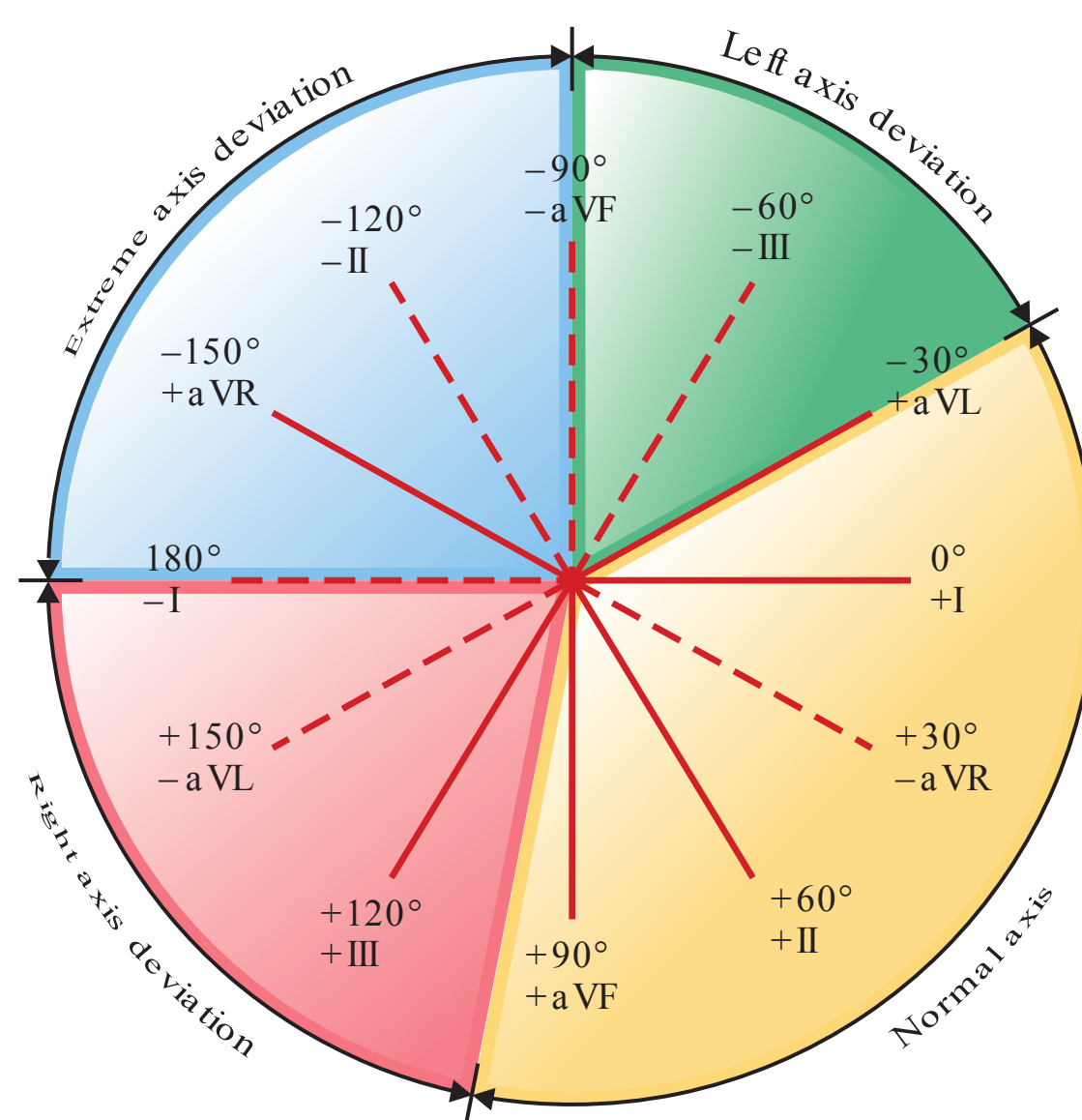


FIGURE 26

13. The answer is D.

(Chap. 11) The ECG exhibits classic findings of a right bundle branch block with an rSR' in V_1 and broad-based terminal S wave in I, II, and V_6 . Left bundle branch block would have a similarly wide QRS, but with the terminal deflections on the QRS occurring with a leftward and posterior vector leading to a large R pattern in I and V_6 and a QS pattern in V_1 . S1Q3T3 is a nonspecific ECG finding for right heart strain and is not present in this ECG. P-pulmonale is a term used to indicate right atrial abnormality or enlargement, seen on ECG as a tall P wave in lead II or V_1 (>2.5 mm). First-degree heart block is seen as a PR interval >200 ms (one large box on a standard-speed ECG).

14. The answer is B.

(Chap. 11) This is a normal 12-lead ECG. The heart rate is about 75 bpm. The P-wave morphology and axis are normal, indicating normal atrial size and activation. The QRS axis is 70 degrees, which is normal. QRS duration is 0.08 seconds (normal), and QT interval 0.36 seconds (normal). There is no abnormal ST elevation or depression, and the T-wave morphology and size are normal.

15. The answer is E.

(Chap. 50) Mr. Wilson is suffering an acute inferolateral myocardial infarction (MI). Note the ST elevations in the inferior leads (II, III, aVF) and in V_6 (lateral precordial lead). Also, the striking ST depressions in the anterior precordial leads (V_1 – V_4) are indicative of posterior ischemia. Here, the presence of ST depressions in an anterior lead represents the “mirror” of ST elevations in a posterior location. One can visualize the ECG pattern in the anterior leads upside

down to see the reciprocal nature of the ST depressions. Although on initial glance, the QRS pattern appears wide in the anterior leads suggesting ventricular tachycardia, on further examination, there are P waves present that are associated with each QRS (seen most clearly in leads II and V_1); thus, the rhythm is sinus tachycardia. The wide appearance of the QRS is due to the striking ST deviation.

16. The answer is B.

(Chap. 50) This patient has an acute anterolateral myocardial infarction. Although it is possible that both the left anterior descending (LAD) and left circumflex (LCx) arteries have coronary disease, concomitant total occlusion of the LAD and LCx arteries would most likely lead to death by either pump failure or malignant ventricular arrhythmia because the left ventricle would have very little blood flow. It is more likely that the proximal LAD (before the first diagonal branch) is occluded. The ST elevations in the anterior leads (V_1 – V_4) and lateral leads (I and aVL) with reciprocal depressions in the inferior leads (II, III, and aVF) implicate the LAD. This patient has also developed Q waves in the anterior leads (V_2 and V_3), indicating the prolonged nature of the coronary occlusion in this man presenting 3 hours after the onset of pain.

17. The answer is A.

(Chap. 50) This ECG demonstrates sinus rhythm with premature atrial contractions (not normal sinus rhythm; note the fifth and ninth beats occurring early and preceded by an abnormal P wave indicating atrial origin). Also, the QRS is wide and in a right bundle branch block (RBBB) pattern as indicated by the large terminal R wave in the anterior

precordial leads and broad-based terminal S wave in the lateral limb leads (I and aVL). In the presence of an RBBB, T waves in the anterior lead are often inverted and do not indicate acute ischemia. No premature ventricular contractions are present in this ECG. However, Q waves are present in the anterior precordial leads (V_1 – V_3) so that the usual RBBB rsR' is simply a qR pattern, indicating a prior anterior-septal myocardial infarction.

18. The answer is D.

(Chaps. 50) This patient has pericarditis. Often associated temporally with a viral upper respiratory infection, pericarditis is a common noncoronary cause of chest pain. The ECG is confirmatory of the history, showing diffuse, concave ST elevations with PR depressions in most leads. Lead aVR shows PR-segment elevation typical of acute pericarditis. Options A and C would be appropriate choices if the patient were having an acute myocardial infarction. Option E would not be appropriate in the immediate setting of myocardial infarction or pericarditis. Patients with pericarditis without signs of elevated intrapericardial pressure (elevated neck veins, tachycardia, low blood pressure, elevated pulsus paradoxus) or suspicion of purulent pericarditis (fever, sepsis) do not require an echocardiogram (option B). Treatment of acute viral or idiopathic pericarditis is with nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine.

19. The answer is B.

(Chap. 50) This patient likely missed a session of hemodialysis due to the impassible roads. In this setting and in combination with the tall, peaked T waves seen on the ECG, one would suspect hyperkalemia. Hyponatremia does not have a stereotypical finding on ECG. Hypercalcemia causes a shortened QT interval (usually due to a shortening specifically of the ST segment with T waves of normal duration). This patient also likely has hypocalcemia evidenced by the prolonged QT interval on ECG. The hypocalcemia in this case is due to hyperphosphatemia secondary to missed hemodialysis. Hypokalemia causes prolonged QT interval, low T-wave voltage, and often the presence of U waves. Hypomagnesemia likewise causes a prolongation of the QT interval and increases the risk of torsades de pointes.

20. The answer is E.

(Chap. 51) This patient demonstrates findings consistent with cardiac amyloidosis. The greatly thickened myocardium with a bright or “sparkly” appearance, left atrial enlargement, and impressive clinical heart failure in the setting of preserved systolic function all suggest infiltrative cardiomyopathy. Strain echocardiographic imaging often reveals decreased myocardial strain and strain rates with relative sparing of the apex in amyloidosis. Atrial fibrillation is common in patients with cardiac amyloidosis and

carries a high risk of thromboembolic complications. The preserved ejection fraction renders ischemic disease (as evaluated by positron emission tomography [PET] stress) less likely. Although *Trypanosoma cruzi* (the etiologic agent of Chagas disease) is endemic in many South American countries, cardiac manifestations include a dilated cardiomyopathy with conduction disease as opposed to a restrictive, thickened myocardium. In the evaluation for cardiac amyloidosis, a reasonable first step is a serologic evaluation for a paraproteinemia with protein electrophoreses of the serum and urine and a light chain assay. Negative results do not rule out amyloidosis, and an endomyocardial biopsy is warranted if clinical suspicion is high enough. If a light chain paraproteinemia is confirmed, a bone marrow biopsy may be warranted later to evaluate for multiple myeloma or a plasma cell dyscrasia. Another common cause of cardiac amyloidosis is deposition of transthyretin (TTR or prealbumin) protein, either in the familial or senile forms. If amyloidosis is confirmed on biopsy and mass spectroscopy cannot be performed or suggests TTR deposition, then genetic testing for known mutations in the *TTR* gene would be warranted for prognosis and future genetic counseling should be offered to the patient and their family.

21. The answer is A.

(Chap. 51) This image shows reversible ischemia in all segments of the apex, the distal inferior wall, and the mid to distal septal and inferior walls. This is compatible with ischemic in the distal LAD territory. Ischemia due to significant left main coronary artery stenosis can lead to a “pseudonormal” pattern on nuclear perfusion stress tests, due to balanced ischemia and equally depressed blood flow through the entire left ventricle. Transient dilatation with stress is an important clue to the presence of balanced ischemia and may point toward left main or “triple-vessel” coronary disease. Ischemia of the left circumflex artery would spare the septum and cause reversible ischemia in the lateral and perhaps inferior walls. The right coronary artery and posterior descending artery would present with ischemia of the proximal inferior wall with variable involvement of the inferoseptal segments.

22. The answer is E.

(Chap. 15) Many cells in the heart possess the ability to spontaneously depolarize due to slow spontaneous diastolic depolarization (phase 4). The SA node, AV node, and Purkinje cells all possess this ability. However, in normal physiologic states, the SA node possesses the “steepest” phase 4 slope and thus depolarizes more rapidly than any other potential pacemaker cells. The location does not determine the SA node’s pacemaker ability, and the SA nodal cells have no intercalated discs. Phase 0 is actually slower in nodal cells than in ventricular or atrial nonnodal cells (Figure 27).

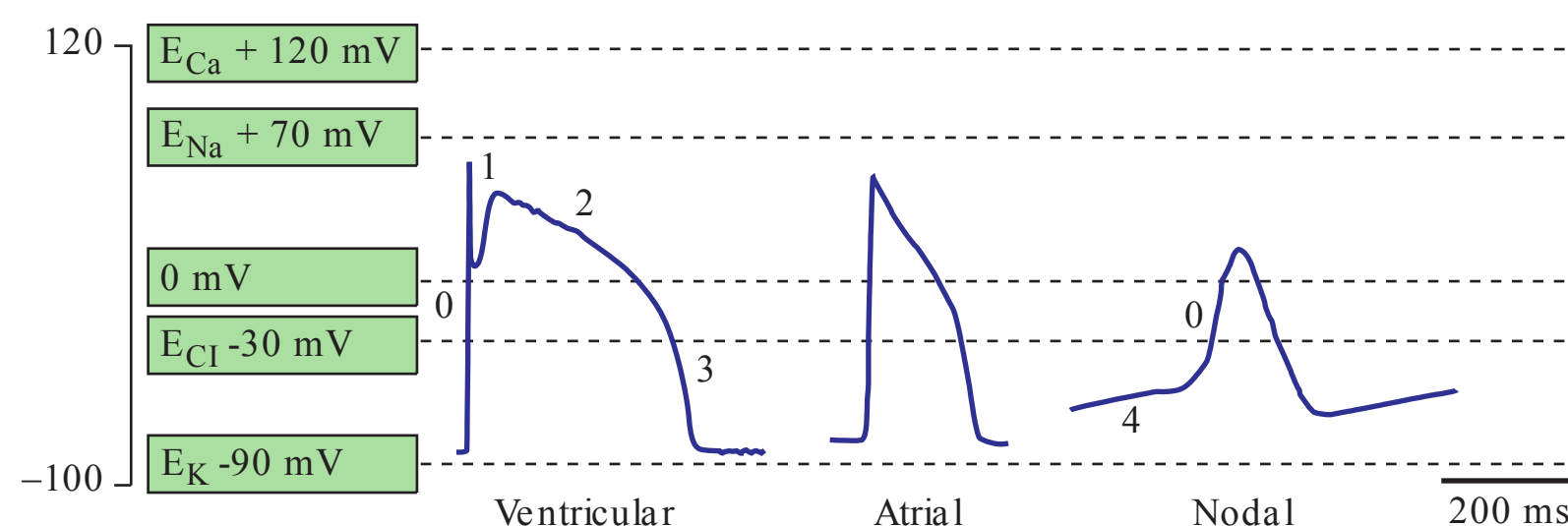


FIGURE 27

23. The answer is C.

(Chap. 15) Sinus bradycardia and pauses up to 3 seconds are common in young individuals, particularly in highly trained athletes. Given the normal conduction intervals on his baseline ECG, lack of symptoms, and normal physical examination, no further testing is warranted. It is clear that he has the ability to augment his heart rate if he has been training for this race.

24. The answer is D.

(Chap. 15) Determining the intrinsic heart rate (IHR) may distinguish SA node dysfunction from slow heart rates that result from high vagal tone. The normal IHR after administration of 0.2 mg/kg of propranolol and 0.04 mg/kg of atropine is $117.2 - (0.53 \times \text{age})$ in bpm; a low IHR is indicative of SA disease. For this patient, his IHR should be approximately 85 bpm. Electrophysiologic testing may play a role in the assessment of patients with presumed SA node dysfunction and in the evaluation of syncope, particularly in the setting of structural heart disease. In this circumstance, electrophysiologic testing is used to rule out more malignant etiologies of syncope, such as ventricular tachyarrhythmias and AV conduction block. There are several ways to assess SA node function invasively. They include the sinus node recovery time (SNRT), which is defined as the longest pause after cessation of overdrive pacing of the right atrium near the SA node (normal: <1500 ms). This patient has no evidence of tachyarrhythmias (option E) or atrial fibrillation (option B). While amyloid cardiomyopathy might explain SA nodal dysfunction, further evidence (endomyocardial biopsy or serologic evidence of light chain disease) would be required to make this diagnosis.

25. The answer is E.

(Chap. 15) Sinoatrial dysfunction is often divided into intrinsic disease and extrinsic disease of the node. This is a critical distinction, because extrinsic causes are often reversible and pacemaker placement is not required. Drug toxicity is a common cause of extrinsic, reversible sinoatrial dysfunction, with common culprits including β -blockers, calcium channel blockers, lithium toxicity, narcotics, pentamidine, and clonidine. Hypothyroidism, sleep apnea, hypoxia, hypothermia, and increased intracranial pressure are all also reversible forms of extrinsic

dysfunction. Radiation therapy can result in permanent dysfunction of the node and therefore is an irreversible, or intrinsic, cause of SA node dysfunction. In symptomatic patients, pacemaker insertion may be indicated.

26. The answer is B.

(Chap. 15) The tachycardia-bradycardia variant of sick sinus syndrome is associated with an increased risk of thromboembolism particularly when similar risk factors are present that increase the risk of thromboembolism in patients with atrial fibrillation. Specific risk factors associated with highest risk include age >65 years, patients with prior history of stroke, valvular heart disease, left ventricular dysfunction, or atrial enlargement. Patients with these risk factors should be treated with anticoagulation.

27. The answer is A.

(Chap. 16) AV nodal transitional connections may exhibit decremental conduction, defined as slowing of conduction with increasingly rapid rates of stimulation. This property of the AV node is physiologically important. If a very rapid atrial arrhythmia occurs, the AV node acts as a sort of “gatekeeper” to the ventricles due to its decremental conduction. Thus, in the case of atrial fibrillation (where atrial rates often exceed 300 bpm), the ventricular rate never approaches these very rapid rates. Some accessory conduction pathways, in contrast, do not exhibit decremental conduction properties and will rapidly conduct tachycardias (such as atrial fibrillation) to the ventricles, leading to hemodynamic collapse.

28. The answer is E.

(Chap. 16) The compact AV node ($\sim 1 \times 3 \times 5 \text{ mm}^3$) is situated at the apex of the triangle of Koch, which is defined by the coronary sinus ostium posteriorly, the septal tricuspid valve annulus anteriorly, and the tendon of Todaro superiorly. The compact AV node continues as the penetrating AV bundle where it immediately traverses the central fibrous body and is in close proximity to the aortic, mitral, and tricuspid valve annuli; thus, it is subject to injury in the setting of valvular heart disease or its surgical treatment. It is common for patients to experience transient AV block after valve surgery (particularly aortic valve surgery) due to the surrounding edema. Many patients will

regain normal conduction as the perioperative injury and edema decrease; however, some patients will not and will require permanent pacemaker placement. It is unlikely that this patient has developed new systemic disease such as Lyme disease, sarcoidosis, or endocarditis. SA nodal disease would manifest as sinus bradycardia, which this patient does not have.

29. The answer is A.

(Chap. 16) Congenital AV block in the setting of a structurally normal heart has been seen in children born to mothers with systemic lupus erythematosus (SLE). SLE can cause sterile endocarditis in adults but is not common in children of mothers with SLE. Similarly, early-onset coronary artery disease, pulmonary hypertension, and occasionally cardiomyopathy are described in SLE patients but not in their children just after birth.

30. The answer is E.

(Chap. 16) This patient has Mobitz II, second-degree AV block. This particular ECG demonstrates a specific pattern of this called paroxysmal AV block. This is p and the patient's concerning symptoms of recurrent syncope indicate significant conduction disease and warrant urgent permanent pacemaker implantation. SA node block would be

indicated on the surface ECG by the absence of P waves (and SA node potentials might be noted on invasive intracardiac electrograms). First-degree AV block would manifest as a prolonged PR interval (>200 ms) without any nonconducted beats. Atropine (anticholinergic) administration can sometimes help differentiate between Mobitz I (usually intranodal disease) and Mobitz II (usually infranodal disease) block when the ECG is not clear. Since the AV node is more heavily innervated by vagal efferents, atropine will improve the block in Mobitz I but worsen it in Mobitz II infranodal disease. The converse is largely true of maneuvers that increase vagal tone (carotid sinus massage or Valsalva).

31. The answer is C.

(Chap. 16) Mobitz I (Wenckebach) AV block is a very common phenomenon in young, healthy adults, particularly during sleep and in patients with high vagal tone such as trained athletes. Given his reassuring lack of symptoms, no further testing or intervention is needed for this patient. The indications for pacemaker implantation in AV block are noted in Table 2. Note that asymptomatic type I second-degree AV block is a class III recommendation (recommended against).

TABLE 2 Guideline Summary for Pacemaker Implantation in Acquired AV Block

Class I

1. First-degree or high-grade AV block at any anatomic level associated with:
 - a. Symptomatic bradycardia
 - b. Essential drug therapy that produces symptomatic bradycardia
 - c. Periods of asystole >3 seconds or any escape rate <40 bpm while awake, or an escape rhythm originating below the AV node
 - d. Postoperative AV block not expected to resolve
 - e. Catheter ablation of the AV junction
 - f. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy, regardless of the presence of symptoms
2. Second-degree AV block with symptomatic bradycardia
3. Type II second-degree AV block with a wide QRS complex with or without symptoms
4. Exercise-induced second- or third-degree AV block in the absence of ischemia
5. Atrial fibrillation with bradycardia and pauses >5 seconds

Class IIa

1. Asymptomatic third-degree AV block regardless of level
2. Asymptomatic type II second-degree AV block with a narrow QRS complex
3. Asymptomatic type II second-degree AV block with block within or below the His at electrophysiologic study
4. First- or second-degree AV block with symptoms similar to pacemaker syndrome

Class IIb

1. AV block in the setting of drug use/toxicity, when the block is expected to recur even with drug discontinuation
2. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of AV block regardless of the presence of symptoms

Class III

1. Asymptomatic first-degree AV block
2. Asymptomatic type I second-degree AV block at the AV node level
3. AV block that is expected to resolve or is unlikely to recur (Lyme disease, drug toxicity)

Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

32 and 33. The answers are B and D, respectively.

(Chap. 17) The patient has persistent, non–life-threatening palpitations that distress her enough to seek medical attention. A continuous Holter monitor for 24 hours is appropriate for patients in whom the symptoms happen several times over 24 hours, whereas an event monitor is triggered by the patient when symptoms occur and thus can be worn for longer period of time, which is appropriate in this patient. There is no indication of gastrointestinal triggers, so abdominal computed tomography (CT) would not be helpful. The atrial premature contractions are uncomplicated, do not require additional diagnostic evaluation at this time, and pose no additional health risk. Electrophysiology (EP) referral is indicated for patients with life-threatening or severe symptoms such as syncope.

34. The answer is D.

(Chap. 17) Wolff-Parkinson-White (WPW) pattern is almost always due to accessory pathway conduction whereby electrical signals are able to propagate from atria to ventricles without first going through the AV node. As opposed to the AV node, many accessory pathways fail to exhibit decremental conduction (a slowing of conduction at increasing rates of excitation) and thus are able to rapidly conduct fast atrial rhythms to the ventricles. At exceedingly fast rates (as might be present in atrial fibrillation), this can lead to cardiovascular collapse. The observation that Ms. Milsap's delta wave disappears and QRS complex normalizes at a relatively high heart rate is reassuring. In that case, the accessory pathway cannot conduct antegrade at a rate >120 bpm and is unlikely to cause serious tachyarrhythmia. The ability to augment a rapid sinus rhythm is normal for her age and does not carry any particular prognosis. The location of the accessory pathway in a septal position makes it somewhat more difficult to ablate with catheters, and the operator must take care to avoid the native AV node and His-Purkinje system. The ability of the accessory pathway to conduct both antegrade and retrograde makes it a substrate for atrioventricular reentrant tachycardia (AVRT).

35. The answer is A.

(Chap. 17) Adenosine is a powerful “nodal-blocking agent”; that is, it blocks propagation of electrical signal through the AV node. It has a very short half-life. Administration of adenosine to a patient in atrial fibrillation will induce a transient complete heart block but will not stop the atrial fibrillation. When the adenosine wears off in a few seconds and AV conduction resumes, the ventricular rhythm will again be irregularly irregular. All the other choices have been shown to achieve sinus rhythm better than placebo in patients with atrial fibrillation.

36. The answer is D.

(Chap. 17) This patient has new atrial fibrillation. When one assesses a patient with new atrial fibrillation, it is prudent to proceed through a series of decisions systematically. If

the patient is hemodynamically unstable (low blood pressure, pulmonary edema, poor mentation, low urine output), then urgent direct current cardioversion is warranted. This patient is clearly stable. The next decision hinges around rate versus rhythm control. Several studies have shown clinical equipoise between rate and rhythm control strategies, with patients randomized to the rhythm control strategies undergoing far more procedures and taking more medications than patients randomized to the rate control strategies. This is also true in heart failure patients. Given the lack of symptoms and already controlled resting heart rate, rhythm control with either medications (amiodarone) or cardioversion is not a class I indication. In fact, a type I antiarrhythmic such as flecainide would be contraindicated for this patient because it has been shown to increase mortality in patients with coronary disease. The final question revolves around anticoagulation. Patients with atrial fibrillation have varying degrees of risk of thromboembolic events. Patients are stratified into risk categories by assessing set risk factors. One can remember the CHADS₂ mnemonic to recall each point of the risk scoring system (congestive heart failure [CHF], hypertension, age >75, diabetes, and stroke/cerebrovascular accident [which receives 2 points]). A more sensitive score includes vascular disease, age >65, and female sex (CHADS-VASc). Any combined score >1 warrants systemic anticoagulation. Patients with a score of 0 do not require systemic anticoagulation and can take full-strength aspirin. A score of 1 is intermediate and requires an in-depth discussion with the patient about their risk threshold for anticoagulation. Many experts recommend systemic anticoagulation with a CHADS₂ score of 1. This patient has a CHADS₂ score of 3 (CHF, hypertension, age) and thus warrants systemic anticoagulation.

37. The answer is D.

(Chap. 17) This patient has classic symptoms for an AV nodal reentrant tachycardia. The so-called frog sign (prominent venous pulsations in the neck due to cannon A waves seen in AV dissociation) on physical examination is frequently present and suggests simultaneous atrial and ventricular contraction. First-line therapy for these reentrant narrow complex tachyarrhythmias is carotid sinus massage to increase vagal tone. Often this is all that is required to return the patient to sinus rhythm. If that is not successful, intravenous (IV) adenosine 6–12 mg may be attempted. If adenosine fails, IV β -blockers or calcium channel blockers may be used (diltiazem or verapamil). Finally, in hemodynamically compromised patients or those who have failed to respond to previous measures, direct current (DC) cardioversion with 100–200 J is indicated.

38. The answer is B.

(Chap. 17) The AFFIRM and RACE trials compared outcomes in survival and thromboembolic events in patients with atrial fibrillation using two treatment strategies: rate control and anticoagulation versus pharmacotherapy to

maintain sinus rhythm. There was no difference in events in the two groups, which was thought to be due to the inefficiencies of pharmacotherapy, with over half of patients failing drug therapy, and also the high rates of asymptomatic atrial fibrillation in the sinus rhythm group. Thus, when considering discontinuation of anticoagulation in patients who have maintained sinus rhythm, it is recommended to place a prolonged ECG monitor to ensure that asymptomatic atrial fibrillation is not present. Because of the risk of QT prolongation and polymorphic ventricular tachycardia, dofetilide and sotalol are recommended to be initiated in the hospital.

39. The answer is E.

(Chap. 17) This rhythm is multifocal atrial tachycardia (MAT), which is easily confused with atrial fibrillation due to its irregularly irregular nature. However, MAT is distinguished by the multiple different P waves present (at least three different P-wave morphologies). MAT is classically present in patients with severe pulmonary disease and is exacerbated in the presence of acute illness. No anticoagulation is needed for MAT, and DC cardioversion is not efficacious. Some patients respond to the nondihydropyridine calcium channel blockers (diltiazem and verapamil), and amiodarone has some limited effect. In this patient, controlling the underlying cause of her tachycardia (pain and dehydration) is the most appropriate first therapy.

40. The answer is D.

(Chap. 17) This patient is unstable with hypotension and poor cerebral perfusion due to her wide complex tachycardia. Defibrillation is the only therapy that is appropriate and should be performed immediately.

41. The answer is A.

(Chap. 17) This ECG shows a wide complex, irregularly irregular tachycardia. Ventricular tachycardia is wide complex but is regular. Unless there is underlying conduction system disease (such as a left bundle branch block, which is unusual in a young patient), AV nodal reentry tachycardia (AVNRT), AVRT, and atrial flutter are also narrow complex and are regular. The irregularly irregular rhythm coupled with the extremely fast ventricular rate make the diagnosis of atrial fibrillation with antegrade conduction down an accessory pathway most likely. If no accessory pathway is present, the decremental conduction properties of the AV node will limit ventricular response rate. However, some accessory pathways do not have decremental conduction properties, and thus pass every atrial impulse through to the ventricle. In the setting of atrial rates above 300 (as in atrial fibrillation), this can be catastrophic.

42. The answer is C.

(Chap. 18) This is idioventricular rhythm, which is a rhythm originating in the ventricular myocardium but with a rate <100 bpm. This rhythm, also known as accelerated

idioventricular rhythm, is commonly seen after successful reperfusion and requires no specific therapy. Normal sinus rhythm is ruled out by the absence of P waves. Ventricular tachycardia requires a heart rate of >100 bpm for diagnosis. A junctional escape would likely be narrow (unless there is aberrant conduction) and much slower (40–60 bpm). Atrial fibrillation would be irregularly irregular.

43. The answer is B.

(Chap. 18) This ECG shows a slow, sinusoidal ventricular rhythm. This bizarre rhythm is almost always due to drug effects or electrolyte disturbances. Specifically, this represents the most extreme ECG changes of hyperkalemia. Unfortunately, the scenario in this question is all too common in patients on hemodialysis who cannot or do not go to dialysis sessions. Hyperkalemia is a dreaded complication of missed dialysis and can be deadly. Hyperphosphatemia and resultant hypocalcemia can also be caused by missed hemodialysis sessions. These do not cause the observed ECG changes. Although defibrillation is appropriate, one should realize that it may not be effective until the hyperkalemia is controlled. Temporizing measures such as IV calcium, insulin and dextrose, bicarbonate, and inhaled β -agonists can be used to lower the serum potassium while emergent hemodialysis is readied.

44. The answer is E.

(Chap. 18) Although it is true that patients with cardiomyopathy and nonsustained ventricular tachycardia (NSVT) or a high burden of premature ventricular contractions (PVCs) have a higher mortality, multiple studies have found no mortality benefit to suppressing the ventricular arrhythmias with antiarrhythmic medications. In fact, the CAST trial showed that the use of Vaughn-Williams class I drugs such as flecainide and propafenone increased mortality when used in patients with PVCs and ischemic disease. Thus, these are contraindicated in patients with any structural heart disease. Implantable defibrillator therapy is not warranted in this patient for primary prevention despite the presence of NSVT. It would be prudent to ensure that her electrolytes are normal given her recent diuresis; hypokalemia in particular is associated with an increased burden of PVCs and NSVT.

45. The answer is A.

(Chap. 18) For survivors of an acute MI, an implantable cardioverter defibrillator (ICD) reduces mortality in certain high-risk groups: patients who have survived >40 days after the acute MI and have a left ventricular (LV) ejection fraction of ≤ 0.30 or who have an ejection fraction <0.35 and have symptomatic heart failure (functional class II or III). Thus, early ICD implantation is not warranted here. In patients >5 days after MI with NSVT and inducible sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) on electrophysiologic studies, an automatic ICD may be considered. Angiotensin-converting enzyme (ACE)

inhibitors, β -blockers, and eplerenone (aldosterone antagonists) have all been shown to reduce early mortality in patients after an anterior MI with reduced ejection fraction.

46. The answer is E.

(Chap. 18) This patient has a subset of idiopathic VT, or VT originating in the absence of structural or inheritable cardiac disease. The presence of a normal baseline ECG, echocardiogram, and cardiac magnetic resonance imaging (MRI) essentially rule out Brugada syndrome, arrhythmogenic right ventricular dysplasia, and hypertrophic cardiomyopathy (although these are all important considerations in the patients with ventricular arrhythmias at a young age). The pictured ECG is classic for right ventricular outflow tract (RVOT) VT with a left bundle branch block pattern (indicating origin in the RV) and inferior axis (indicating origin in the cranial part, or base, of the heart). LV intraventricular VT is another idiopathic VT, but presents with a right bundle branch block pattern. RVOT VT is often induced by scenarios with sympathetic nervous system activation, such as singing a solo in front of a crowd. This arrhythmia is not associated with sudden cardiac death and often responds to β -blockers or nondihydropyridine calcium channel blockers. Catheter ablation is an option if medical therapy fails to control the symptoms or is not desired.

47. The answer is D.

(Chap. 18) This patient has medication-induced long QT syndrome (methadone and erythromycin are common causes) and resulting torsades de pointes (TdP). Sustained TdP is never a perfusing rhythm and can rapidly degenerate into ventricular fibrillation. For nonsustained TdP, correction of hypokalemia and expeditious administration of IV magnesium may lead to cessation of the arrhythmia. If this fails, administration of isoproterenol or pacing to a rate of 100–120 bpm will suppress PVCs and lead to rate-dependent shortening of the QT interval, thereby suppressing TdP and allowing time for the medications to washout. Inducing bradycardia (with metoprolol) or further QT prolongation with amiodarone may be harmful and lead to more TdP. Defibrillation is not warranted in NSVT. Likewise, ICD implantation is not necessary given that this is a secondary phenomenon due to drug interaction. This patient should be very cautious to avoid QT-prolonging agents in the future, however, and should consider transitioning off methadone at the earliest chance.

48. The answer is A.

(Chap. 18) Atrial-ventricular dissociation is a classic finding in ventricular tachycardia. Physical examination may show jugular vein cannon waves when the atria contract against a closed tricuspid valve, and the ECG will manifest this with atrial capture and/or fusion beats. Other findings on ECG of ventricular tachycardia include QRS duration >140 ms for right bundle branch pattern in V_1 or >160 ms for left bundle morphology in lead V_1 , frontal

plane axis -90 to 180 degrees, delayed activation during initial phase of the QRS complex, and bizarre QRS pattern that does not mimic typical right or left bundle branch block QRS complex patterns. An irregularly irregular rhythm with changing QRS complexes suggests atrial fibrillation with ventricular preexcitation. Carotid sinus massage, aimed at increasing vagal tone and slowing AV node conduction, is not effective at slowing ventricular tachycardia because the reentrant focus is below the AV node.

49. The answer is E.

(Chap. 52) This ECG demonstrates sinus arrhythmia, a normal physiologic finding particularly in young adults. During inspiration, the sinus rate speeds up to maintain cardiac output in the face of a slightly decreased left ventricular stroke volume, and vice versa during expiration. This is a normal, healthy heart rhythm and requires no further investigation or intervention.

50. The answer is A.

(Chap. 52) This ECG shows 2:1 second-degree AV block; that is, there are two P waves for every QRS complex. In this type of second-degree AV block, it can be difficult to tell the difference between type I (Wenckebach) block, which is usually anatomically located at the AV node, and type II block, which is often infranodal in origin. There is no progressively prolonging or stable PR interval to distinguish. However, the presence of a narrow, normal QRS complex is sufficient to make Wenckebach block most likely, particularly in an athletic young person during sleep, a time of high vagal tone. A wide QRS complex during 2:1 conduction, particularly in a patient in whom infranodal disease would be likely, is concerning for second-degree type II block and more concerning for progression to complete or high-grade heart block.

51. The answer is B.

(Chap. 52) In heart block occurring at the AV node, the administration of atropine (an anticholinergic agent) will often improve the block as the AV node has a high degree of vagal efferent innervation. The SA node phase 4 action potential slope will increase as well with anticholinergic stimulation, causing faster sinus rate. In heart block occurring below the AV node, anticholinergic stimulation will often cause the appearance of a worse (3:1, 4:1, etc.) heart block as the sinus rate increases and more impulses are transmitted to the infranodal tissue during its prolonged (and unchanged with atropine) refractory period. One may use this finding to differentiate Wenckebach and type II second-degree heart block during difficult-to-interpret 2:1 conduction.

52. The answer is E.

(Chap. 52) This ECG illustrates tremor artifact, most notable in leads I, III, and aVL (thus making it likely that the tremor is occurring in the left arm). It is easy to confuse

tremor artifact with atrial flutter or atrial fibrillation. Note the normal sinus P waves in lead II and all the precordial leads. No further testing is needed for this ECG.

53. The answer is E.

(Chap. 52) The ECG shows atrial flutter, with 2:1 conduction and the typical atrial rate of 300 bpm and ventricular rate of 150 bpm. The saw-tooth baseline pattern, best appreciated in the inferior leads, is a clue that this atrial flutter is “typical,” or due to a macro-reentrant circuit that relies on the cavo-tricuspid isthmus. As such, it is quite amenable to ablation with a >95% success rate. However, given that Mr. Tillman’s symptoms have been ongoing for >48 hours, he is at risk for development of an atrial thrombus (similar to in atrial fibrillation) and thus requires systemic anticoagulation before achievement of sinus rhythm. He will also likely require a transesophageal echocardiogram to ensure that no clot exists prior to ablation or cardioversion. Aspirin is not adequate to prevent potential embolization. Atrial flutter will generally not convert in response to amiodarone, digoxin, or other medications. Given the absence of heart failure, there is no indication for furosemide.

54. The answer is E.

(Chap. 52) The ECG is diagnostic of Wolff-Parkinson-White syndrome and likely explains the patient’s palpitations. The presence of a left bundle–appearing delta wave/QRS complex (large R in the lateral precordial leads, I, and aVL) localizes this accessory tract to the right ventricle. Another clue is the exceedingly short PR interval; the ventricle is very preexcited as the sinus impulse arrives at the right ventricle very early because the accessory tract is so close to the SA node. Left-sided bypass tracts tend to appear slightly less preexcited (somewhat longer PR interval and slightly less wide QRS). Also, more tellingly, left-sided accessory tracts have a right bundle–like appearance with negative QRS complexes in the lateral precordial leads and lead I. Septal bypass tracts can be difficult to localize and are hallmarked by a rapid transition in QRS vector between the anterior precordial leads (V_1 and V_2 most often).

55. The answer is C.

(Chap. 19) The New York Heart Association (NYHA) classification is a tool to define criteria that describe the functional ability and clinical manifestations of patients in heart failure. It is also used in patients with pulmonary hypertension. These criteria have been shown to have prognostic value with worsening survival as class increases. They are also useful to clinicians when reading studies to understand the entry and exclusion criteria of large clinical trials. Class I is used for patients with no limiting symptoms; class II for patients with slight or mild limitation; class III implies no symptoms at rest but dyspnea, angina, or palpitations with little exertion, and patients are moderately limited; class IV is severely limited, so that even minimal activity

causes symptoms. Treatment guidelines also frequently base recommendations on these clinical stages. The patient has symptoms with mild exertion but is comfortable at rest; therefore, he is NYHA class III.

56. The answer is E.

(Chap. 19) The patient presents with evidence of heart failure by history, and physical examination confirms this diagnosis. The warm extremities make a high-output state more likely than low cardiac output. Physical examination also shows exophthalmos and a fine tremor suggestive of hyperthyroidism. Thyrotoxicosis, along with anemia, nutritional disorders, and systemic arteriovenous shunting, can all cause high-output heart failure. The eye examination and tremor make hyperthyroidism more likely than anemia. Although systolic and diastolic dysfunction are more common causes of heart failure, disorders associated with a high-output state are often reversible, and therefore, a diagnosis should be pursued when clinical clues suggest this may be present.

57. The answer is A.

(Chap. 19) Coronary artery disease remains the leading cause of heart failure with reduced ejection fraction, accounting for >60% of cases. Among all patients with heart failure, approximately 50% will have a preserved ejection fraction (LV ejection fraction [LVEF] >50%; option E). Although medical and device therapy has greatly advanced in the preceding decades, prognosis for heart failure patients remains grim. Community studies have shown that 30%–40% of patients die within 1 year of diagnosis and 60%–70% die within 5 years. The prognosis becomes even more dire in patients with extreme exertional limitation. NYHA class IV patients have a 50%–70% 1-year mortality (option C). Increasingly, epidemiologic data are showing that genetic cardiomyopathy (or familial cardiomyopathy) is more common than previously believed. It is now thought that >20% of all nonischemic cardiomyopathies are genetic or familial in etiology (option D). Although anemia is often an exacerbating factor in patients who already have heart failure, it is quite rare for it to cause de novo heart failure in a patient with a structurally normal heart (option B).

58. The answer is C.

(Chap. 19) In the failing heart, multiple systems are upregulated to attempt to maintain cardiac output through augmenting sodium and water retention (angiotensin II, aldosterone, arginine vasopressin) and myocardial contractility (norepinephrine). Although initially helpful in maintaining cardiac output, these adaptations become deleterious in contributing to the development of adverse myocardial remodeling and the congestive state. Also deleterious is the upregulation of inflammatory systems (including tumor necrosis factor). Counterregulatory natriuretic peptides (such as B-type natriuretic peptide [BNP]) are also upregulated and aid in reducing systemic

vascular resistance and natriuresis. In the state of heart failure, transcriptional and posttranscriptional changes in the myocyte lead to calcium leakage through the sarcoplasmic reticular membrane and, therefore, decreased calcium uptake in the sarcoplasmic reticulum.

59. The answer is E.

(Chap. 19) Orthopnea, which is defined as dyspnea occurring in the recumbent position, is usually a later manifestation of heart failure than is exertional dyspnea. It results from redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbency, with a resultant increase in pulmonary capillary pressure. Nocturnal cough is a common manifestation of this process and a frequently overlooked symptom of heart failure. Orthopnea generally is relieved by sitting upright or sleeping with additional pillows. Although orthopnea is a relatively specific symptom of heart failure, it may occur in patients with abdominal obesity or ascites and in patients with pulmonary disease whose lung mechanics favor an upright posture (such as with respiratory muscle compromise). In contrast, the hepatopulmonary syndrome is characterized by the development of pulmonary arteriovenous malformations and thus multiple shunts within the pulmonary circulation. These tend to develop in the lung bases, and thus, the patient's shunt fraction increases with an upright posture. This leads to orthodeoxia (hypoxia in the upright position) and platypnea (the sensation of shortness of breath when upright) rather than orthopnea.

60. The answer is C.

(Chap. 19) BNP and its NT terminal fraction are increased in heart failure states and, on the population level, contribute to prognosis in heart failure states. However, it is important to recognize that natriuretic peptide levels increase with age and renal impairment, are more elevated in women, and can be elevated in right heart failure from any cause. Levels can be falsely low in obese patients. Other biomarkers such as soluble ST-2 and galectin-3 are newer biomarkers that can be used to determine the prognosis of heart failure patients.

61. The answer is A.

(Chap. 19) The right heart is a thin-walled compliant chamber that is better suited to handle volume overload than pressure overload. In the setting of acute pressure overload (massive pulmonary embolism), the right heart quickly dilates and fails, leading to circulatory collapse. In the setting of slowly developing pulmonary hypertension (due to vascular, thrombotic, or pulmonary disease), the right heart hypertrophies in an attempt to compensate. Over time, the right ventricular (RV) contractile function becomes uncoupled from an ever-increasing afterload, and cor pulmonale or RV failure develops. In a patient with preexisting cor pulmonale, small changes in RV preload or afterload can be catastrophic. In this patient, any change leading to acidemia

(reducing respiratory rate) or elevated alveolar pressures (increasing positive end-expiratory pressure, increasing tidal volume) are likely to increase RV afterload and may worsen RV stroke volume and cardiac output. Incidentally, increasing transmural pressure (plateau or end-expiratory ventilator pressures) has disparate effects on RV and LV afterload. Because the RV target vasculature is completely intrathoracic, the pressure is transmitted across the vessel walls and must be overcome by the RV. However, LV vasculature is mostly extrathoracic. Thus, the increased intrathoracic pressure is only transmitted to the LV and actually reduces afterload (transmural chamber pressure). Hypoxia causes pulmonary vasoconstriction (as opposed to the systemic circulation, where it causes vasodilation). Thus, increasing the FiO_2 in an attempt to improve the hypoxia may reduce the pulmonary vasoconstriction and lower the RV afterload.

62. The answer is E.

(Chap. 20) While therapeutic targets in heart failure with reduced ejection fraction (HFrEF) are relatively abundant and guided by the targets of disease modification, trials in heart failure with preserved ejection fraction (HFpEF) have been largely disappointing. ACE inhibitors (option A) have been studied in many mechanistic studies and have shown no convincing mortality benefit. Similarly, angiotensin receptor blockers (option B) were studied in the CHARM-Preserved and I-PRESERVE studies and were found to have no mortality benefit. Sildenafil (a phosphodiesterase-5 inhibitor) was shown to improve filling pressures and RV function in patients with HFpEF, but did not show mortality benefit. Finally, digoxin, which inhibits sodium-potassium-ATPase, was shown to have no role in treating HFpEF in the DIG study. Overall, symptom management and blood pressure control are the goals in HFpEF treatment now. One should also remain vigilant for myocardial ischemia.

63. The answer is B.

(Chap. 20) This patient clearly has adequate cardiac output to maintain peripheral perfusion as evidenced by her physical examination (warm extremities) and adequate blood pressure. However, her elevated creatinine is vexing and indicates that she suffers from the cardiorenal syndrome. In some cases, it truly is a depressed cardiac output causing a low glomerular filtration rate (GFR); however, these cases are typically accompanied by other signs of peripheral malperfusion. In most cases when cardiac output is not severely depressed, it is thought that a complex interplay of elevated venous pressures (reducing transglomerular perfusion pressures) and abdominal pressures leads to decreased GFR. In these cases, reducing venous pressures with diuretics is the most reasonable first option. In patients who respond poorly (rising creatinine or adverse hemodynamic effects), hemodynamic monitoring (option A) or ultrafiltration can be considered. Digoxin should be used with caution in renal insufficiency and has

no real benefit acutely here. In cases where cardiac output is thought to be severely depressed and peripheral perfusion is compromised, inotropic therapy may be indicated.

64. The answer is D.

(Chap. 20) Nesiritide is the recombinant form of human BNP. It was introduced in a fixed dose for therapy of acute decompensated heart failure after demonstration of a more rapid and greater reduction in pulmonary capillary wedge pressure than with intravenous nitrates. Enthusiasm for nesiritide waned due to concerns within the pivotal trials for development of renal insufficiency and an increase in mortality. To address these concerns, a large-scale morbidity and mortality trial, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), was completed in 2011 and randomly enrolled 7141 patients with acute decompensated heart failure to nesiritide or placebo for 24–168 hours in addition to standard care. Nesiritide was not associated with an increase or a decrease in the rates of death and rehospitalization and had a clinically insignificant benefit on dyspnea. Renal function did not worsen, but increased rates of hypotension were noted. Although this trial established the safety of nesiritide, its routine use cannot be advocated due to lack of significant efficacy.

65. The answer is E.

(Chaps. 19 and 20) The utility of invasive hemodynamic monitoring during acute decompensated heart failure has been highly scrutinized recently. Based on several observational and randomized trials, the routine use of a pulmonary artery catheter is not recommended and should be restricted to patients who respond poorly to diuresis or experience hypotension or signs and symptoms suggestive of a low cardiac output where therapeutic targets are unclear. In this patient with hypotension and signs of low cardiac output, invasive monitoring will allow the clinician to rapidly, objectively assess any changes in hemodynamic status and respond appropriately. In states of “cold” (poor perfusion) and “wet” (elevated filling pressures, or hypervolemia) heart failure, the stroke volume and cardiac output are decreased. Left ventricular stroke work index (a calculated value that normalizes left ventricular work for the patient’s body surface area and afterload) is also diminished. Mixed venous oxygen saturation is greatly diminished as well, as the Fick equation dictates that cardiac output is proportional to the venous oxygen saturation if oxygen consumption and arterial oxygen saturation are normal. Systemic vascular resistance equals the mean systemic arterial pressure minus the mean right atrial pressure divided by cardiac output. As cardiac output drops, the systemic vasculature will increase its resistance to attempt to maintain blood pressure and end-organ perfusion pressure. However, this initially compensatory action becomes deleterious because an inefficient left ventricle must work against an ever-increasing afterload. The most effective

inotropic agents in acute decompensated heart failure (milrinone, and dobutamine) also have vasodilatory properties to combat this harmful systemic vascular resistance (SVR) increase.

66. The answer is C.

(Chap. 20) β -Blockers represent the most-studied drug in the history of HFrEF. Initially avoided for their negative inotropic and chronotropic effects, they now form the foundation of neurohormonal-targeted therapy in the treatment of chronic HFrEF. However, the benefit of β -blockers is not a blanket class effect and indeed has only been demonstrated for three drugs in the numerous clinical trials: metoprolol succinate, bisoprolol, and carvedilol. Importantly, metoprolol tartrate has never been found to have mortality benefit in HFrEF, nor have β -blockers with intrinsic sympathomimetic activity (nebivolol, xamoterol).

67. The answer is E.

(Chap. 20) Whether β -blockers or ACE inhibitors should be started first was answered by the Cardiac Insufficiency Bisoprolol Study (CIBIS) III, in which outcomes did not vary when either agent was initiated first. Thus, it matters little which agent is initiated first; what does matter is that optimally titrated doses of both ACE inhibitors and β -blockers are established in a timely manner. It should be noted that although ACE inhibitors have been shown to have a dose-dependent reduction in hospitalizations, higher tolerated doses do not materially improve survival. In contrast, β -blockers have a strong dose effect on survival. Thus, if forced to choose between a higher dose of β -blockers or ACE inhibitor due to low blood pressure, the higher dose of β -blocker may provide more survival benefit.

68. The answer is E.

(Chap. 20) This patient is on optimal doses of the three medications forming the foundation of neurohormonal therapy for HFrEF. Digoxin was shown to reduce hospitalizations but not mortality in the DIG trial. The addition of valsartan to ACE inhibitor therapy was studied in the Val-HEFT trial and showed a trend toward worse outcomes. Similarly, aliskiren (a direct renin inhibitor) was studied in addition to ACE inhibitors in the ASTRONAUT trial and showed no mortality benefit and an abundance of side effects such as hyperkalemia and hypotension. Ivabradine, a novel heart rate-reducing agent, was studied in the SHIFT trial and showed mortality benefit, but only in patients with a heart rate >70 bpm already on β blockers. This patient’s heart rate is controlled.

69. The answer is A.

(Chap. 20) Sudden cardiac death due to ventricular arrhythmias is the mode of death in approximately half of patients with heart failure and is particularly proportionally prevalent in patients diagnosed with HFrEF in early stages of the disease. Although primary prevention of sudden cardiac

death is challenging, the two most important risk markers for increased risk of death are the degree of residual left ventricular dysfunction despite optimal medical therapy ($\leq 35\%$) and the underlying etiology of heart failure (postmyocardial infarction or ischemic cardiomyopathy). Currently, patients with NYHA class II to III symptoms of heart failure and an LVEF $< 35\%$, irrespective of etiology of heart failure, are appropriate candidates for implantable cardioverter defibrillator (ICD) prophylactic therapy. In patients with a history of myocardial infarction and optimal medical therapy with residual LVEF $\leq 30\%$ (even when asymptomatic), placement of an ICD is appropriate. The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) both sought to use cardiac resynchronization therapy (CRT) in combination with an ICD. Most benefit in mildly symptomatic HFrEF patients accrues from applying this therapy in those with a QRS width of > 149 ms and a left bundle branch block pattern. Attempts to further optimize risk stratification and expand indications for CRT using modalities other than electrocardiography have proven disappointing. Likewise, surgical ventricular remodeling was studied in a 1000-patient trial and found to have no disease-modifying effect. It is still used, but relegated to patients with cardioembolic strokes on anticoagulation or patients with refractory ventricular arrhythmias. Ivabradine, a novel heart rate–reducing agent, may reduce mortality in patients with HFrEF who have a resting heart rate > 70 bpm while on an adequate dose of a β -blocker.

70. The answer is D.

(Chap. 21) In patients with an orthotopic heart transplant, the donor heart is denervated during the harvest. In the absence of sympathetic or parasympathetic innervation, many patients exhibit a mild resting tachycardia or slightly elevated heart rate. Heart rate response during exercise or physiologic stress may be delayed, but is enacted by cardiac response to circulating catecholamines, primarily adrenal in origin. It is important to realize this to avoid unnecessary testing and to avoid adverse events with drug administration. In particular, atropine will have almost no effect on a patient after orthotopic heart transplant, and extreme caution should be exercised in administering adenosine because the denervated heart may have a very delayed recovery from adenosine-induced heart block.

71. The answer is D.

(Chap. 21) In the United States, the allocation of donor organs is accomplished under the supervision of the United Network for Organ Sharing, a private organization under contract to the federal government. The United States is divided geographically into 11 regions for donor heart allocation. Allocation of donor hearts within a region is decided according to a system of priority that takes into account (1) the severity of illness, (2) the geographic distance from the

donor, and (3) the patient's time on the waiting list. A physiologic limit of ~ 3 hours of “ischemic” (out-of-body) time for hearts precludes a national sharing of hearts. The allocation system design is reissued annually and is responsive to input from a variety of constituencies, including both donor families and transplantation professionals.

72. The answer is C.

(Chap. 21) Despite usually having young donor hearts, cardiac allograft recipients are prone to develop coronary artery disease (CAD). The CAD is generally a diffuse, concentric, and longitudinal process that is quite different from “ordinary” atherosclerotic CAD, which is more focal and often eccentric. The underlying etiology most likely is primarily immunologic injury of the vascular endothelium, but a variety of risk factors influence the existence and progression of CAD, including nonimmunologic factors such as dyslipidemia, diabetes mellitus, and cytomegalovirus (CMV) infection (as in this patient). It is hoped that newer and improved immunosuppressive modalities will reduce the incidence and impact of these devastating complications, which currently account for the majority of late posttransplantation deaths. Thus far, the immunosuppressive agents mycophenolate mofetil and the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus have been shown to be associated with short-term lower incidence and extent of coronary intimal thickening; in anecdotal reports, institution of sirolimus was associated with some reversal of CAD. The use of statins also is associated with a reduced incidence of this vasculopathy, and these drugs are now used almost universally in transplant recipients unless contraindicated. Palliation of CAD with percutaneous interventions is probably safe and effective in the short term, although the disease often advances relentlessly. Because of the denervated status of the organ, patients rarely experience angina pectoris, even in advanced stages of disease. Antibody (humoral)–mediated rejection is exceedingly rare in a patient this far out from transplant, particularly one who fortunately has had no prior rejection episodes. While cellular rejection is possible, the presence of a normal left ventricle (and no arrhythmias) makes it less likely. Tacrolimus most commonly causes hypertension, neurologic complications, and renal insufficiency. Mycophenolate mofetil most commonly causes bone marrow suppression and diarrhea. Low-dose prednisone is generally well tolerated, although chronic steroids carry incipient risk of diabetes, obesity, skin changes, iatrogenic adrenal insufficiency, osteoporosis, and cataracts. None of these drugs classically causes dyspnea.

73. The answer is C.

(Chap. 21) For patients with end-stage cardiomyopathy (NYHA class IV or peak oxygen consumption < 14 mL/kg/min), the prognosis is abysmal. In the landmark REMATCH trial, the 2-year survival of the medically treated arm was only 8%. Orthotopic heart transplantation is the gold standard therapy for these patients. However, some patients are

not candidates due to underlying comorbidities that would render a transplantation too dangerous. For these patients, the continuous flow left ventricular assist devices have been shown convincingly to improve mortality (2-year survival in REMATCH was ~ 60% and has improved since that study). Although it is unreasonable to predict a complication-free course (most patients have thrombotic, infectious, or neurologic complications during their course of support), the median survival for patients with left ventricular assist device support is now approaching 5 years. Stem cell therapy is currently investigational only and has never been shown to meaningfully impact survival. Similarly, milrinone or dobutamine therapy (inotropic support) can be used continuously to support quality of life as a palliative goal or as a bridge to initiation of mechanical support or transplantation. However, all studies show that the use of inotropes negatively impacts survival.

74. The answer is B.

(Chap 22) The most common birth defects are cardiovascular in origin. These malformations are due to complex multifactorial genetic and environmental causes. Recognized chromosomal aberrations and mutations of single genes account for <10% of all cardiac malformations. Congenital heart disease (CHD) complicates ~1% of all live births in the general population—about 40,000 births per year—but occurs more frequently in the offspring (about 4%–10%, depending on maternal CHD type) of women with CHD. Due to the remarkable surgical advances over the last 60 years, >90% of affected neonates and children now reach adulthood; women with CHD may now frequently successfully bear children after competent repairs. As such, the population with CHD is steadily increasing. Women with CHD are at increased risk for peri- and postpartum complications, but maternal CHD is generally not considered an absolute contraindication to pregnancy unless the mother has certain high-risk features (e.g., cyanosis, pulmonary hypertension, decompensated heart failure, arrhythmias, aortic aneurysm).

75. The answer is D.

(Chap. 21) Atrial septal defect (ASD) is a common cardiac anomaly that may be first encountered in the adult and occurs more frequently in females. Sinus venosus ASD occurs high in the atrial septum near the entry of the superior vena cava into the right atrium and is associated frequently with anomalous pulmonary venous connection from the right lung to the superior vena cava or right atrium. Ostium primum ASDs lie adjacent to the atrioventricular valves, either of which may be deformed and regurgitant. Ostium primum ASDs are common in Down syndrome, often as part of complex atrioventricular septal defects with a common atrioventricular valve and a posterior defect of the basal portion of the interventricular septum. The most common ostium secundum ASD involves the fossa ovalis and is mid-septal in location; this should

not be confused with a patent foramen ovale (which is present in ~25% of healthy adults). Anatomic obliteration of the foramen ovale ordinarily follows its functional closure soon after birth, but residual “probe patency” is a common normal variant; ASD denotes a true deficiency of the atrial septum and implies functional and anatomic patency.

76. The answer is D.

(Chap. 21) This patient has a small muscular VSD. The decision on whether to treat a VSD is complex but is based on the principle of avoiding any right ventricular and pulmonary vascular compromise. Similarly, one must avoid repairing a VSD in the setting of overt pulmonary hypertension, as this is clearly associated with worse outcomes. Closure is not recommended for patients with normal pulmonary arterial pressures with small shunts (pulmonary-to-systemic flow ratios of <1.5:1). Operative correction or transcatheter closure is indicated when there is a moderate to large left-to-right shunt with a pulmonary-to-systemic flow ratio >1.5:1, in the absence of prohibitively high levels of pulmonary vascular resistance (pulmonary arterial resistance is less than two-thirds of systemic arterial resistance). This patient has a normal pulmonary artery pressure, a pulmonary vascular resistance to SVR ratio of 0.33, and Qp:Qs of 1.25; therefore, closure is not warranted at this time, but follow-up is indicated.

77. The answer is C.

(Chap. 21) This patient has the classic murmur and findings of myocardial ischemia associated with a spontaneous rupture of a coronary artery aneurysm to form a coronary arteriovenous fistula. In this case, the presence of an oxygenation step-up in the right heart, with near-systemic oxygenation levels in the coronary sinus (which usually has very low oxygen saturation levels), makes this diagnosis certain. An ASD would not present with such a murmur or clinical presentation. A VSD would not show such high oxygen levels in the coronary sinus. A patent ductus arteriosus can present with a similar murmur but usually causes left-to-right shunting at the level of the pulmonary artery; thus, the oxygen step-up would be there. Anomalous left coronary artery off the pulmonary artery causes myocardial ischemia, although not so precipitously and usually early in life, and is not associated with a murmur. In this condition, oxygenated blood from the aortic root flows via a dilated right coronary artery and collaterals to the left coronary artery and retrograde to the lower pressure pulmonary artery circulation via the anomalous left main coronary artery (which emerges from the pulmonary artery). Most patients die in the first year of life from myocardial ischemia and fibrosis, although a minority can live into adulthood.

78. The answer is A.

(Chap. 22) Bicuspid aortic valve is among the most common of congenital heart cardiac abnormalities. Valvular function is often normal in early life and thus may escape

detection. Due to abnormal flow dynamics through the bicuspid aortic valve, the valve leaflets can become rigid and fibrosed, leading to either stenosis or regurgitation. However, pathology in patients with bicuspid aortic valve is not limited to the valve alone. The ascending aorta is often dilated, misnamed “poststenotic” dilatation; this is due to histologic abnormalities of the aortic media and may result in aortic dissection. It is important to screen specifically for aortopathy because dissection is a common cause of sudden death in these patients.

79. The answer is D.

(Chap. 22) The four classic components of the tetralogy of Fallot are malaligned VSD, obstruction to RV outflow, aortic override of the VSD, and RV hypertrophy (due to the RVs response to aortic pressure via the large VSD). Tricuspid atresia is associated with Ebstein anomaly and hypoplastic right heart syndrome. In these cases, a concurrent systemic-to-pulmonary connection is required to maintain early life (such as a patent ductus arteriosus). Right heart bypass operations such as the Glenn shunt or Fontan palliation can provide adequate pulmonary flow to support patients into and through early adulthood.

80. The answer is B.

(Chap. 23) The patient has aortic stenosis that presented late in life. Although bicuspid aortic valve underlies nearly half of all aortic stenosis cases, this lesion typically presents earlier in life, and only 40% of patients >70 years old with aortic stenosis who undergo surgery have a bicuspid valve. Rheumatic heart disease may cause aortic stenosis, but nearly invariably, mitral stenosis is also present. Underlying connective tissue disease is not known to be associated with aortic stenosis. Modern research on development of aortic stenosis has shown that several traditional atherosclerotic risk factors are present such as diabetes mellitus, smoking, chronic kidney disease, and the metabolic syndrome. Polymorphisms of the vitamin D receptor have also been demonstrated in patients with symptomatic aortic stenosis.

81. The answer is C.

(Chap. 23) Exertional syncope is a late finding in aortic stenosis and portends a poor prognosis. Patients with this symptom or with angina pectoris have an average time to death of 3 years. Patients with dyspnea have an average time to death of 2 years, and patients with heart failure have an average time to death of 1.5–2 years. Given these data, patients with severe aortic stenosis and symptoms should strongly be considered for surgical therapy.

82. The answer is D.

(Chap 23) This patient is in cardiogenic shock due to his progressive aortic stenosis (AS). The natural history of symptomatic severe AS is not encouraging. Aortic valve area, on average, declines by 0.1 cm^2 per year, and gradient

increases by 7 mmHg annually. The average time to death after the onset of various symptoms is as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; and congestive heart failure, 1.5–2 years. Moreover, in >80% of patients who die with AS, symptoms had existed for <4 years. Currently, this patient has compromised organ function due to the severe LV obstruction of AS and resultant low stroke volume. Any negative inotropic or chronotropic agents may prove fatal, as reducing heart rate or stroke volume will further compromise cardiac output (option C). Digoxin is unlikely to augment stroke volume to any significant degree in the setting of severe AS and is risky in the setting of compromised renal function (option B). Although statins have been shown to slightly slow the progression of AS, they serve no role in the acute setting (option A). Phenylephrine is an α -agonist. Although it may serve to increase blood pressure, it acts via peripheral vasoconstriction, which further increases the resistance the left ventricle is working against. Percutaneous aortic balloon valvuloplasty (PABV) is a poor long-term therapeutic option because almost all patients have the recrudescence of severe AS within 6 months to a year. However, PABV can serve as bridge to definite therapy (such as surgical aortic valve replacement), temporarily improving cardiac output and end-organ perfusion to render surgical risk acceptable. Other options would be an intra-aortic balloon pump or, in rare cases, mechanical circulatory support.

83. The answer is D.

(Chap. 23) This patient has evidence of the clinical entity referred to as low-gradient, low-flow AS. Conceptually, the aortic valve area during systole is dependent on two factors: (1) aortic valve morphology (e.g., calcific AS with restricted leaflet motion), and (2) ventricular contractile force. Even a normal aortic valve will open very little if the ventricle contracts very weakly. In this patient's case, the finding of a low calculated aortic valve area without a severely high gradient (severe is >40 mmHg) in the setting of reduced LV function defines the entity of low-gradient, low-flow AS. It is difficult to determine whether the valve area is low due to reason 1 or 2 during a resting echocardiography. However, dobutamine stress will accomplish two goals. First, it will assess for ventricular viability (the ability to increase stroke volume by 20%), which is shown to predict outcomes after aortic valve replacement. Second, and more importantly, as the ventricular contractility increases, it allows the clinician to differentiate between true, morphologic AS and the appearance of AS due to compromised ventricular function (termed pseudo-AS). Although the other options may aid in other facets of this patient's management, none will allow the clinician to make this differentiation.

84. The answer is A.

(Chap. 27) An increase in the LV end-diastolic volume (increased preload) constitutes the major hemodynamic

compensation for aortic regurgitation (AR); thus, preload is increased. The total LV stroke volume also increases to attempt to maintain effective LV stroke volume (total LV stroke volume – regurgitant volume). To do this, the LV must dilate. As the LV dilates, the wall tension to develop a given systolic blood pressure must increase as dictated by LaPlace's law, and thus, afterload is increased. During diastole, as a large volume of blood leaves the systemic circulation to regurgitate into the LV, the diastolic pressure falls, often equilibrating with the LV pressure in severe cases. Coronary perfusion occurs primarily during diastole and depends on the gradient between aortic pressure and LV pressure through the coronaries. This explains why patients with severe AR may manifest anginal symptoms.

85. The answer is C.

(Chap. 23) This patient has severe, acute AR and indeed warrants emergent surgery. Note that her murmur is very quiet and short. In the setting of acute, severe valvular regurgitant lesions, the pressure gradient between the two chambers (in this case, the aorta and LV) quickly equilibrates during the regurgitant period. Sometimes, patients with these lesions can have no audible murmur at all, making diagnosis challenging. In this case, the goal is to reduce the regurgitant volume and thus increase effective stroke volume (total stroke volume – regurgitant volume). Interventions that increase systemic vascular resistance (vasopressin or norepinephrine) will increase regurgitant volume. Likewise, because aortic regurgitation occurs during diastole, interventions that increase diastolic time (e.g., β -blockers) will also worsen regurgitant volume. Because intra-aortic balloon pumps inflate during diastole, they will also worsen regurgitation from aorta to LV and are contraindicated in moderate or worse AR. Nitroprusside will reduce systemic vascular resistance and thus reduce the driving pressure for regurgitation. Careful administration of nitroprusside, often with concomitant invasive hemodynamic monitoring, may stabilize organ perfusion and allow surgical correction. It is important to realize that no medical therapy will correct this abnormality; surgical correction is the only definitive therapy.

86. The answer is E.

(Chap. 24) Rheumatic fever remains the leading cause of mitral stenosis (MS). Other less common etiologies of obstruction to LV inflow include congenital mitral valve stenosis, cor triatriatum, mitral annular calcification with extension onto the leaflets, systemic lupus erythematosus, rheumatoid arthritis, left atrial myxoma, and infective endocarditis with large vegetations. Pure or predominant MS occurs in approximately 40% of all patients with rheumatic heart disease and a history of rheumatic fever. In other patients with rheumatic heart disease, lesser degrees of MS may accompany mitral regurgitation and aortic valve disease.

87. The answer is B.

(Chap 24) In MS, the flow obstruction between the left ventricle and left atrium creates elevated left atrial pressure to maintain cardiac output. For example, once the effective mitral valve orifice reaches 1.5 cm^2 , the left atrial pressure must be $>25 \text{ mmHg}$ to maintain a normal cardiac output. LV preload, diameter, and end-diastolic pressure are normal or diminished in MS. Similarly, cardiac output is normal or diminished. Due to elevated left atrial pressures, pulmonary venous pressures rise. This causes pulmonary vascular congestion and distention and reduces pulmonary vascular compliance.

88. The answer is C.

(Chap 24) MS represents a fixed obstructive lesion between the left atrium and ventricle. Because flow across this valve occurs in diastole, any intervention that shortens diastole will cause worsened obstruction and more elevated left atrium pressures. Thus, tachycardia induced by exercise or β -agonists is detrimental in MS. Metoprolol, a β -antagonist, will not shorten diastole. Additionally, any extra volume load or higher demand for cardiac output, as in anemia, will lead to an elevated left atrial pressure. The extra blood volume of pregnancy can be particularly poorly tolerated in patients with significant MS.

89. The answer is D.

(Chap. 24) The left atrial to left ventricular pressure gradient is highly dependent on heart rate because diastolic duration is inversely related to heart rate. In the setting of MS, a long diastolic time allows more time for the left atrium to empty and thus lower pressures. Hence, sinus bradycardia is advantageous in the setting of MS, and inducing a faster heart rate via pacemaker would be harmful. The loss of atrial systole during atrial fibrillation is often poorly tolerated in MS, and regaining sinus rhythm would undoubtedly lower atrial pressure. However, the vast majority of patients with MS are unable to maintain sinus rhythm over the long term because their atria tend to be very dilated. Diuretics and percutaneous mitral valvotomy will both lower left atrial pressure.

90. The answer is C.

(Chap. 24) This patient has asymptomatic moderate MS (severe is valve area $<1.5 \text{ cm}^2$). There is no evidence that the procedural mitral valve repair improves the prognosis of patients with slight or no functional impairment. Therefore, unless recurrent systemic embolization or severe pulmonary hypertension has occurred (pulmonary artery systolic pressures $>50 \text{ mmHg}$ at rest or $>60 \text{ mmHg}$ with exercise), valvotomy is not recommended for patients who are entirely asymptomatic and/or who have mild or moderate stenosis (mitral valve area $>1.5 \text{ cm}^2$). Given this patient's lack of symptoms and relatively low resting heart rate, β -blockade is not warranted. Similarly, sildenafil (a pulmonary vasodilator) will not help reduce pulmonary pressures.

91. The answer is B.

(Chap. 24) Mitral regurgitation (MR) occurs due to several reasons. Distinction should be drawn between primary (degenerative, organic) MR, in which the leaflets and/or chordae tendineae are primarily responsible for abnormal valve function, and functional (secondary) MR, in which the leaflets and chordae tendineae are structurally normal but the regurgitation is caused by annular enlargement, papillary muscle displacement, leaflet tethering, or their combination. This patient has functional MR due to his nonischemic dilated cardiomyopathy. In such patients, particularly those with an ejection fraction (EF) $<30\%$, there is concern that repairing the mitral valve will lead to an overall increase in LV afterload and worsening of LV function. It is important to realize that the state of MR is one of very low afterload for the LV because it can eject easily into the low-pressure, compliant left atrium. Thus, even a slight reduction in EF ($<60\%$) can represent significant LV dysfunction that can be unmasked after mitral valve repair. In patients with ischemic MR and significantly impaired LV systolic function (EF $<30\%$), the risk of surgery is higher, recovery of LV performance is incomplete, and long-term survival is reduced. Referral for surgery must be individualized and made only after aggressive attempts with guideline-directed medical therapy and cardiac resynchronization therapy, when indicated. The routine performance of valve repair in patients with significant MR in the setting of severe, functional, nonischemic dilated cardiomyopathy (such as this patient) has not been shown to improve long-term survival compared with optimal medical therapy. Percutaneous therapy is currently under investigation for patients with functional MR but has not yet been shown to improve survival.

92. The answer is D.

(Chap 25) Note the gradient between right atrial pressure and right ventricular end-diastolic pressure (15 and 6 mmHg, respectively) and the left atrium (represented by the pulmonary capillary wedge pressure) and left ventricular end-diastolic pressure (12 and 6 mmHg, respectively). This is diagnostic of mixed tricuspid and mitral stenosis. Also note that the gradient between the left atrium and left ventricle is not severe and that the pulmonary arterial and right ventricular pressures are not very elevated. In the presence of tricuspid stenosis, flow is decreased to the pulmonary vasculature and left heart, thus blunting the hemodynamic effects of even severe mitral stenosis. Grading the severity of mitral stenosis in this setting is quite difficult. Finally, this mix of valvular disease is essentially diagnostic of rheumatic disease. The tricuspid valve is never involved alone and is always affected only if the mitral is also involved. Radiation injury and carcinoid syndrome are two other, rarer causes of combined mitral and tricuspid valvular disease.

93. The answer is A.

(Chap. 25) This patient has severe tricuspid regurgitation (TR) secondary to RV dilation and dysfunction, which is in turn secondary to her severe pulmonary arterial hypertension. In cases of functional TR, repair is relegated to instances where surgery is already being pursued for left-sided valvular lesions. Furthermore, the presence of severe pulmonary hypertension is a relative contraindication for TR repair. The RV suddenly finds itself without the “pop-off valve” of severe TR and often fails when faced with the overwhelming afterload of the abnormal pulmonary vasculature. Percutaneous tricuspid valve repair is not currently performed in clinical practice. Balloon valvotomy is a repair for tricuspid stenosis, not regurgitation. There is no indication in this patient for repair of the mitral valve. Patients with mitral valvular disease may develop significant pulmonary hypertension; however, the diagnosis of idiopathic pulmonary arterial hypertension cannot be established until significant mitral valve dysfunction has been ruled out.

94. The answer is C.

(Chap. 25) Pulmonic stenosis is a rare valvular lesion encountered in adults. Fortunately, percutaneous balloon valvotomy often provides a highly efficacious, relatively low-risk therapeutic option. Diuretics can be used to treat symptoms and signs of right heart failure. Provided there is less than moderate pulmonic regurgitation, pulmonic balloon valvotomy is recommended for symptomatic patients with a domed valve and a peak gradient >50 mmHg (or mean gradient >30 mmHg) and for asymptomatic patients with a peak gradient >60 mmHg (or mean gradient >40 mmHg). Surgery may be required when the valve is dysplastic (as seen in patients with Noonan syndrome and other disorders).

95. The answer is D.

(Chap. 26) This patient is in a precarious situation and likely will require emergent surgical intervention to survive. The combination of severe obstruction to LV outflow (severe AS) and acute, severe regurgitant mitral valve disorder will inevitably lead to intractable pulmonary edema and cardiogenic shock unless both structural abnormalities are corrected. At the advent of severe mitral regurgitation, the LV will be more effectively “unloaded” because now it can eject not only against the stenosed aortic valve, but also into the relatively low-pressure left atrium, and thus afterload will decline. Likewise, with more of the stroke volume going ineffectively into the left atrium, the effective stroke volume (total stroke volume – regurgitant volume) will decline. The aortic valve gradient will decline merely because there is less volume going across the aortic valve with each contraction. Likewise, because both the catheter-derived and echocardiographic-derived calculations of aortic valve area are dependent on the gradient for calculation, they will decline. Ejection fraction, however,

will increase as the LV will be better able to contract in the state of relatively lower afterload. This highlights a misconception that higher ejection fraction is always better. LV ejection fraction is highly dependent not only on the contractile state of the ventricle, but also on its afterload state.

96. The answer is D.

(Chap. 26) Patients with valvular atrial fibrillation are at particularly high risk for systemic thromboembolisms, including stroke. In general, unless a direct contraindication is present, these patients warrant systemic anticoagulation. It is important to remember that the novel oral anticoagulants (apixaban, dabigatran, and rivaroxaban), although easier to administer, are not approved for valvular atrial fibrillation. Warfarin remains the best “tried-and-true” option for valvular atrial fibrillation.

97. The answer is C.

(Chap. 27) Peripartum cardiomyopathy is a rare complication of pregnancy and can occur during the last trimester or within the first 6 months postpartum. Risk factors include advanced age, increased parity, twin pregnancy, malnutrition, use of tocolytic therapy for premature labor, and preeclampsia.

98. The answer is D.

(Chap. 27) Cardiac involvement is common in many of the neuromuscular diseases. The ECG pattern of Duchenne muscular dystrophy is unique and consists of tall R waves in the right precordial leads with an R/S ratio >1.0 , often with deep Q waves in the limb and precordial leads. These patients often have a variety of supraventricular and ventricular arrhythmias and are at risk for sudden death due to the intrinsic cardiomyopathy as well as the low ejection fraction. Implantable cardioverter defibrillators should be considered in the appropriate patient. Global left ventricular dysfunction is a common finding in dilated cardiomyopathies, whereas focal wall motion abnormalities and angina are more common if there is ischemic myocardium. This patient is at risk for venous thromboembolism; however, chronic thromboembolism would not account for the severity of the left heart failure and would present with findings consistent with pulmonary hypertension. Amyotrophic lateral sclerosis is a disease of motor neurons and does not involve the heart. This patient would be young for that diagnosis. An advanced atrial septal defect would present with cyanosis and heart failure (Eisenmenger physiology).

99. The answer is B.

(Chap. 27) Most familial cardiomyopathies are inherited in an autosomal dominant pattern, with occasional autosomal recessive and X-linked inheritance. Missense mutations with amino acid substitutions are the most common in cardiomyopathy. Expressed mutant proteins

may interfere with function of the normal allele through a dominant negative mechanism. Mutations introducing a premature stop codon (nonsense) or shift in the reading frame (frameshift) may create a truncated or unstable protein the lack of which causes cardiomyopathy (haploinsufficiency). Deletions or duplications of an entire exon or gene are uncommon causes of cardiomyopathy, except for the dystrophinopathies.

100. The answer is E.

(Chap. 27) All of the tests listed have a role in some patients with newly diagnosed cardiomyopathy. However, only a thyroid-stimulating hormone (TSH) level receives a Level I recommendation from the American College of Cardiology (ACC)/American Heart Association (AHA) for all patients with new cardiomyopathy. All other tests listed are driven by symptoms and signs that are present. Cardiac MRI and erythrocyte sedimentation rate (ESR) levels may help diagnose inflammation in patients who are suspected to have an acute myocarditis or infiltrative disease. Coronary angiography is only recommended for patients with angina, although one must be careful to include dyspnea on exertion as an angina equivalent. Serum iron and transferrin saturation are worth checking in patients suspected of hemochromatosis. Table 3 lists tests available for the initial evaluation of new cardiomyopathy and indicates which receive a Level I recommendation for all patients.

101. The answer is A.

(Chap. 27) This patient presents with a classic history for fulminant viral myocarditis. A small number of patients present with fulminant myocarditis, with rapid progression from a severe febrile respiratory syndrome to cardiogenic shock that may involve multiple organ systems, leading to renal failure, hepatic failure, and coagulopathy. These patients are typically young adults who have recently been dismissed from urgent care settings with antibiotics for bronchitis or oseltamivir for viral syndromes, only to return within a few days in rapidly progressive cardiogenic shock. Prompt triage is vital to provide aggressive support with high-dose intravenous catecholamine therapy and sometimes with temporary mechanical circulatory support. Recognition of patients with this fulminant presentation is potentially lifesaving because more than half can survive, with marked improvement demonstrable within the first few weeks. The ejection fraction function of these patients often recovers to near-normal, although residual diastolic dysfunction may limit vigorous exercise for some survivors. There is no established role for measuring circulating anti-heart antibodies, which may be the result, rather than a cause, of myocardial injury and have also been found in patients with coronary artery disease and genetic cardiomyopathy. There is currently no specific therapy recommended during any stage of viral myocarditis. Large trials

TABLE 3 Initial Evaluation of Cardiomyopathy

Clinical Evaluation
Torough history and physical examination to identify cardiac and noncardiac disorders ^a
Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders, tachyarhythmias, and sudden death
History of alcohol, illicit drugs, chemotherapy or radiation therapy ^a
Assessment of ability to perform routine and desired activities ^a
Assessment of volume status, orthostatic blood pressure, body mass index ^a
Laboratory Evaluation
Electrocardiogram ^a
Chest radiograph ^a
Two-dimensional and Doppler echocardiogram ^a
Magnetic resonance imaging for evidence of myocardial inflammation and fibrosis
Chemistry:
Serum sodium, ^a potassium, ^a calcium, ^a magnesium ^a
Fasting glucose (glycohemoglobin in diabetes mellitus)
Creatinine, ^a blood urea nitrogen ^a
Albumin, ^a total protein, ^a liver function tests ^a
Lipid profile
Thyroid-stimulating hormone ^a
Serum iron, transferrin saturation
Urinalysis
Creatine kinase isoforms
Cardiac troponin levels
Hematology:
Hemoglobin/hematocrit ^a
White blood cell count with differential, ^a including eosinophils
Erythrocyte sedimentation rate
Initial Evaluation When Specific Diagnoses Are Suspected
Titers for infection in the setting of clinical suspicion:
Acute viral (coxsackie, echovirus, influenza)
Human immunodeficiency virus
Chagas (<i>Trypanosoma cruzi</i>), Lyme (<i>Borrelia burgdorferi</i>), toxoplasmosis
Catheterization with coronary angiography in patients with angina who are candidates for intervention ^a
Serologies for active rheumatologic disease
Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications
Screening for sleep-disordered breathing

^aLevel I recommendations from ACC/AHA Practice Guidelines for Chronic Heart Failure in the Adult.

of immunosuppressive therapy for Dallas Criteria–positive myocarditis have been negative.

102. The answer is C.

Chap. 27) Giant cell myocarditis accounts for 10%–20% of biopsy-positive cases of myocarditis. Giant cell myocarditis typically presents with rapidly progressive heart failure and tachyarrhythmias. Diffuse granulomatous lesions are surrounded by extensive inflammatory infiltrate unlikely

to be missed on endomyocardial biopsy, often with extensive eosinophilic infiltration. Associated conditions are thymomas, thyroiditis, pernicious anemia, other autoimmune diseases, and occasionally recent infections. Glucocorticoid therapy is less effective than for sarcoidosis and is sometimes combined with other immunosuppressive agents. The course is generally of rapid deterioration requiring urgent transplantation. Although the severity of presentation and myocardial histology are more fulminant

than with sarcoidosis, the occasional finding of giant cell myocarditis after sarcoidosis suggests that they may, in some cases, represent different stages of the same disease spectrum.

103. The answer is E.

(Chap. 27) Anthracyclines cause characteristic histologic changes of vacuolar degeneration and myofibrillar loss in the heart. Generation of reactive oxygen species involving heme compounds is currently the favored explanation for myocyte injury and fibrosis. Disruption of the large titin protein may contribute to loss of sarcomere organization. Risk for cardiotoxicity increases with higher doses, preexisting cardiac disease, and concomitant chest irradiation. There are three different presentations of anthracycline-induced cardiomyopathy. (1) Heart failure can develop acutely during administration of a single dose but may clinically resolve in a few weeks. (2) Early-onset doxorubicin cardiotoxicity develops in about 3% of patients during or shortly after a chronic course, relating closely to total dose. It may be rapidly progressive but may also resolve to good, but not normal, ventricular function. (3) The chronic presentation differs according to whether therapy was given before or after puberty. Patients who received doxorubicin while still growing may have impaired development of the heart, which leads to clinical heart failure by the time the patient reaches the early twenties. Late after adult exposure, patients may develop the gradual onset of symptoms or an acute onset precipitated by a reversible second insult, such as influenza or atrial fibrillation. Trastuzumab (Herceptin) is a monoclonal antibody that interferes with cell surface receptors crucial for some tumor growth and for cardiac adaptation. The incidence of cardiotoxicity is lower than for anthracyclines when given alone but enhanced by coadministration with them.

104. The answer is B.

(Chap. 28) This patient has a classic case of acute pericarditis, likely secondary due to recent viral infection. His description of the chest pain (positional, pleuritic), examination revealing a classic three-component friction rub, ECG demonstrating diffuse ST elevation with PR depression, and negative cardiac biomarkers are all suggestive of acute pericarditis. There is no specific therapy for acute idiopathic pericarditis, but bed rest and anti-inflammatory treatment with aspirin (2–4 g/d), with gastric protection (e.g., omeprazole 20 mg/d), may be given. If this is ineffective, one of the NSAIDs, such as ibuprofen (400–600 mg tid) or indomethacin (25–50 mg tid), should be tried. In responsive patients, these doses should be continued for 1–2 weeks and then tapered over several weeks. In patients who are unresponsive, colchicine (0.5 mg bid, given for 4–8 weeks) has been found to be effective, not only in acute pericarditis, but also in reducing the risk of recurrent pericarditis. Colchicine is concentrated in and

interferes with the migration of neutrophils, is contraindicated in patients with hepatic or renal dysfunction, and may cause diarrhea and other gastrointestinal side effects. Glucocorticoids (e.g., prednisone 1 mg/kg/d) usually suppress the clinical manifestations of acute pericarditis in patients who have failed therapy with the anti-inflammatory therapies described earlier but appear to increase the risk of subsequent recurrence. Therefore, full-dose corticosteroids should be given for only 2–4 days and then tapered. Anticoagulants should be avoided because their use could cause bleeding into the pericardial cavity and precipitate cardiac tamponade.

105 and 106. The answers are B and E, respectively.

(Chap. 27) This patient has physical examination findings consistent with cardiac tamponade, likely caused by bleeding into the pericardial space induced by anticoagulation in the setting of acute pericarditis. Acute myocardial infarction has been ruled out, so left main coronary artery occlusion, ruptured chordae tendineae (which would be associated with mitral regurgitation and acute pulmonary edema), and ventricular septal defect are unlikely. Acutely, a minimal amount of supranormal pericardial fluid (often ~200 mL) is required to rapidly increase intrapericardial pressure and cause cardiac tamponade. This is a medical emergency, and prompt evaluation with echocardiography and preparation for emergent pericardiocentesis are warranted. The paradoxical pulse (as noted in the question by the vanishing arterial pulse with inspiration) is an important clue to the presence of cardiac tamponade and consists of a greater than normal (10 mmHg) inspiratory decline in systolic arterial pressure. Because both ventricles share a tight incompressible covering (i.e., the pericardial sac), the inspiratory enlargement of the right ventricle in cardiac tamponade compresses and reduces left ventricular volume; leftward bulging of the interventricular septum reduces further the left ventricular cavity as the right ventricle enlarges during inspiration. Thus, in cardiac tamponade, the normal inspiratory augmentation of right ventricular volume causes an exaggerated reduction of left ventricular volume, stroke volume, and systolic pressure. Because immediate treatment of cardiac tamponade may be lifesaving, prompt measures to establish the diagnosis by echocardiography should be undertaken. When pericardial effusion causes tamponade, Doppler ultrasound shows that tricuspid and pulmonic valve flow velocities increase markedly during inspiration, whereas pulmonic vein, mitral, and aortic flow velocities diminish. In tamponade, there is late diastolic inward motion (collapse) of the right ventricular free wall and the right atrium.

107. The answer is D.

(Chap. 28) The ECG in acute pericarditis without massive effusion usually displays changes secondary to acute

subepicardial inflammation. It typically evolves through four stages. In stage 1, there is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V_2 – V_6 , with reciprocal depressions only in aVR and sometimes V_1 . Also, there is depression of the PR segment below the TP segment, reflecting atrial involvement. Usually there are no significant changes in QRS complexes. After several days, the ST segments return to normal (stage 2), and only then, or even later, do the T waves become inverted (stage 3). Weeks or months after the onset of acute pericarditis, the ECG returns to normal (stage 4). In contrast, in acute myocardial infarction, ST elevations are convex, and reciprocal depression is usually more prominent; these changes may return to normal within a day or two. Q waves may develop, with loss of R-wave amplitude, and T-wave inversions are usually seen within hours before the ST segments have become isoelectric. ST-segment elevation in V_2 may be seen in either acute pericarditis or myocardial infarction.

108. The answer is D.

(Chap. 28) The patient's presentation and physical examination are most consistent with the diagnosis of constrictive pericarditis. The most common cause of constrictive pericarditis worldwide is tuberculosis, but given the low incidence of tuberculosis in the United States, constrictive pericarditis is a rare condition in this country. With the increasing ability to cure Hodgkin disease with mediastinal irradiation, many cases of constrictive pericarditis in the United States are in patients who received curative radiation therapy 10–20 years prior. These patients are also at risk for premature coronary artery disease. Risks for these complications include dose of radiation and radiation windows that include the heart. Other rare causes of constrictive pericarditis are recurrent acute pericarditis, hemorrhagic pericarditis, prior cardiac surgery, mediastinal irradiation, chronic infection, and neoplastic disease. Physiologically, constrictive pericarditis is characterized by the inability of the ventricles to fill because of the noncompliant pericardium. In early diastole, the ventricles fill rapidly, but filling stops abruptly when the elastic limit of the pericardium is reached. Clinically, patients present with generalized malaise, cachexia, and anasarca. Exertional dyspnea is common, and orthopnea is generally mild. Ascites and hepatomegaly occur because of increased venous pressure. In rare cases, cirrhosis may develop from chronic congestive hepatopathy. The jugular venous pressure is elevated, and the neck veins fail to collapse on inspiration (Kussmaul sign). Heart sounds may be muffled. A pericardial knock is frequently heard. The third heart sound that occurs 0.09–0.12 seconds after aortic valve closure at the cardiac apex. Right heart catheterization would show the "square root sign" characterized by an abrupt y-descent followed by a gradual rise in ventricular pressure. This finding, however, is not

pathognomonic of constrictive pericarditis and can be seen in restrictive cardiomyopathy of any cause. Echocardiogram shows a thickened pericardium, dilatation of the inferior vena cava and hepatic veins, and an abrupt cessation of ventricular filling in early diastole. Pericardial resection is the only definitive treatment of constrictive pericarditis. Diuresis and sodium restriction are useful in managing volume status preoperatively, and paracentesis may be necessary. Operative mortality ranges from 5% to 10%. Underlying cardiac function is normal; thus, cardiac transplantation is not indicated. Pericardiocentesis is indicated for diagnostic removal of pericardial fluid and cardiac tamponade, which is not present on the patient's echocardiogram. Mitral valve stenosis may present similarly with anasarca, congestive hepatic failure, and ascites. However, pulmonary edema and pleural effusions are also common. Examination would be expected to demonstrate a diastolic murmur, and echocardiogram should show a normal pericardium and a thickened immobile mitral valve. Mitral valve replacement would be indicated if mitral stenosis were the cause of the patient's symptoms.

109. The answer is A.

(Chap. 29) The description of the mass is classic for an atrial myxoma, the most common primary tumor of the heart. More common in women than men and classically diagnosed in the third to sixth decades of life, myxomata can present with widely varying clinical symptoms. Most arise from the atria, and typically arise from the fossa ovalis in the left atrium. Many are asymptomatic. Myxomas typically do not metastasize distantly, and although other malignancies may metastasize to the heart, the constellation of findings and echocardiographic appearance of this lesion are most consistent with primary myxoma (option E). Some patients experience obstructive symptoms similar to mitral stenosis. Other patients will experience embolic events such as this patient. Patients may also have systemic symptoms such as fever, weight loss, cachexia, arthralgias, digital clubbing, Raynaud phenomenon, hypergammaglobulinemia, anemia, polycythemia, leukocytosis, elevated erythrocyte sedimentation rate, thrombocytopenia, and thrombocytosis. Many patients have undergone extensive rheumatologic and infectious disease workup prior to the diagnosis of their myxoma. The location of the mass would be highly unusual for endocarditis, either of the infectious or marantic varieties (options C and D). Catheter-based biopsy is generally avoided due to the high risk of provoked embolization (option B). Surgical removal of a myxoma is indicated regardless of tumor size. Myxoma recurrence rate is very low in sporadic, nonfamilial cases.

110. The answer is C.

(Chap. 29) Malignant melanoma carries the highest relative risk of cardiac metastases, followed by leukemia and

lymphoma. Although the relative risk of cardiac metastases for both lung cancer and breast cancer is lower than melanoma, the absolute number of cases of cardiac metastases from these malignancies is higher due to the high incidence of these cancers. Hepatocellular carcinoma, glioblastoma, and pancreatic adenocarcinoma do not commonly metastasize to the heart. Most patients with cardiac metastases have advanced malignant disease; thus, therapy is generally palliative and consists of treatment of the primary tumor.

111. The answer is E.

(Chap. 29) T is patient has suffered a commotio cordis. In this condition, blunt, nonpenetrating, often innocent-appearing injuries to the chest may trigger ventricular fibrillation even in absence of overt signs of injury. Commotio cordis occurs most often in adolescents during sporting events (e.g., baseball, hockey, football, lacrosse) and probably results from an impact to the chest wall overlying the heart during the susceptible phase of repolarization just before the peak of the T wave. Survival depends on prompt defibrillation. The described trauma in this case is not severe enough to cause aortic dissection or valvular avulsion. T is 12-year-old boy is unlikely to have coronary atherosclerosis susceptible to rupture requiring percutaneous coronary intervention.

112. The answer is A.

(Chap. 30) Diabetes mellitus, both insulin- and non-insulin-dependent, is an independent risk factor for CAD and accounts for 14%–50% of new cases of cardiovascular disease. CAD is by far the most common cause of death in adults with diabetes. The incidence of CAD relates to the duration of diabetes and level of glycemic control, both motivating factors for patients to comply with therapy. Compared to their nondiabetic counterparts, diabetic patients are more likely to have a myocardial infarction, have a greater burden of CAD, have larger infarct size, and have more postinfarct complications, including heart failure, shock, and death. Importantly, diabetic patients are more likely to have atypical ischemic symptoms; nausea, dyspnea, pulmonary edema, arrhythmias, heart block, or syncope may be their anginal equivalent. Additionally, “silent ischemia,” resulting from autonomic nervous system dysfunction, is more common in diabetic patients, accounting for up to 90% of their ischemic episodes.

113. The answer is C.

(Chaps. 30) Mr. Daniels has thiamine deficiency leading to high-output heart failure, a condition known as “wet beriberi.” Although thiamine deficiency is most common in the developing world and in East Asia (where polished rice, which has much of the thiamine removed in processing, provides the bulk of the caloric intake),

it is also seen in developed nations in patients who are alcoholics or who have chronic disease or malnutrition. Due to a reduction in vasomotor tone and resulting drop in systemic vascular resistance, these patients exhibit signs of high-output failure such as wide pulse pressure, tachycardia, bounding pulses, elevated venous filling pressures, pulmonary and peripheral edema, and dilated hearts. LV ejection fraction is often preserved or elevated. Patients with thiamine deficiency also develop glossitis, peripheral neuropathy, and anemia. Interestingly, administration of thiamine can lead to very rapid (12–48 hours) improvement in heart failure symptoms, diuretic and inotrope responsiveness, and LV size. Hypothyroidism, treated with thyroxine, leads to a reduction in cardiac output and heart rate (option D). Folate and vitamin B₁₂ have been implicated in cases of hyperhomocysteinemia, a disorder associated with increased atherosclerotic risk (options A and E). The clinical benefit of normalizing homocysteine levels has not, however, been proven. Penicillamine is used to chelate copper in cases of Wilson disease, which very rarely manifests as infiltrative cardiomyopathy (option B).

114. The answer is D.

(Chaps. 30 and 405) T is patient clearly has symptomatic hypothyroidism confirmed by an elevated thyroid-stimulating hormone level. Cardiac manifestations of hypothyroidism include reductions in cardiac output, stroke volume, heart rate, systolic blood pressure, and pulse pressure. Pericardial effusions are present in about one-third of patients, but rarely progress to tamponade and probably result from increased capillary permeability. Other clinical signs include cardiomegaly, bradycardia, weak arterial pulses, distant heart sounds, and pleural effusions. Although the signs and symptoms of myxedema may mimic those of CHF, in the absence of other cardiac disease, myocardial failure is uncommon. The ECG generally reveals sinus bradycardia and low voltage and may show prolongation of the QT interval, decreased P-wave voltage, prolonged AV conduction time, intraventricular conduction disturbances, and nonspecific ST-T wave abnormalities.

115. The answer is C.

(Chap. 36) An integrated view of experimental results in animals and studies of human atherosclerosis suggests that the “fatty streak” represents the initial lesion of atherosclerosis. These early lesions most often seem to arise from focal increases in the content of lipoproteins within regions of the intima. In particular, the fraction of lipoproteins related to low-density lipoprotein (LDL) that bear apolipoprotein B appears causally related to atherosclerosis. The accumulation of lipoprotein particles may not result simply from increased permeability, or “leakiness,” of the overlying endothelium. Rather, the

lipoproteins may collect in the intima of arteries because they bind to constituents of the extracellular matrix, increasing the residence time of the lipid-rich particles within the arterial wall. Lipoproteins sequestered from (plasma) antioxidants in the extracellular space of the intima become particularly susceptible to oxidative modification, giving rise to hydroperoxides, lysophospholipids, oxysterols, and aldehydic breakdown products of fatty acids and phospholipids. Next, recruitment of leukocytes to the endothelium occurs. The inflammatory cell types typically found in the evolving atheroma include monocyte-derived macrophages. A number of adhesion molecules or receptors for leukocytes expressed on the surface of the arterial endothelial cell probably participate in the recruitment of leukocytes to the nascent atheroma. Once resident within the intima, the mononuclear phagocytes mature into macrophages and become lipid-laden foam cells, a conversion that requires the uptake of lipoprotein particles by receptor-mediated endocytosis.

116. The answer is B.

(Chap. 36) Atherosclerotic lesions occur ubiquitously in Western societies, and the prevalence of this disease is on the rise globally. Most atheromata produce no symptoms, and many never cause clinical manifestations. Numerous patients with diffuse atherosclerosis may succumb to unrelated illnesses without ever having experienced a clinically significant manifestation of atherosclerosis. Arterial remodeling during atheroma formation accounts for some of this variability in the clinical expression of atherosclerotic disease. During the

initial phases of atheroma development, the plaque usually grows outward, in an abluminal direction. Vessels affected by atherogenesis tend to increase in diameter, a phenomenon known as compensatory enlargement, a type of vascular remodeling. The growing atheroma does not encroach on the arterial lumen until the burden of atherosclerotic plaque exceeds ~40% of the area encompassed by the internal elastic lamina. Flow-limiting stenoses commonly form later in the history of the plaque. Many such plaques cause stable syndromes such as demand-induced angina pectoris or intermittent claudication in the extremities. In the coronary circulation and other circulations, even total vascular occlusion by an atheroma does not invariably lead to infarction. The hypoxic stimulus of repeated bouts of ischemia characteristically induces formation of collateral vessels in the myocardium, mitigating the consequences of an acute occlusion of an epicardial coronary artery.

117. The answer is B.

(Chap. 36) The most recent 2013 ACC/AHA guidelines for cholesterol management have described only four classes of patients who derive definite benefit from statin therapy. These are described in Table 4. While elevated high-sensitivity C-reactive protein has been shown to identify patients at increased risk for atherosclerotic cardiovascular disease (ASCVD), the guidelines do not recommend it as an identifier of patients who are in a definite statin benefit group. However, it can be used to help decide on statin therapy for patients at intermediate risk for ASCVD.

TABLE 4 Summary of the Four Statin Benefit Groups Described in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

- Clinical ASCVD “secondary prevention”
- LDL-C ≥ 190 mg/dL without secondary cause (e.g., saturated/trans fats, drugs, certain diseases)
- Primary prevention with diabetes mellitus: age 40–75 years, LDL-C 70–189 mg/dL
- Primary prevention without diabetes mellitus: age 40–75 years, LDL-C 70–189 mg/dL, estimated ASCVD risk $\geq 7.5\%$

Abbreviations: ACC/AHA, American College of Cardiology and American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Source: Adapted from NJ Stone et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *J Am Coll Cardiol* 63:2889, 2014.

118. The answer is E.

(Chap. 36) As the prevalence of metabolic syndrome and diabetes increases, many patients present with low concentrations of high-density lipoprotein (HDL) cholesterol (<1.0 mmol/L [<40 mg/dL]). A baseline measurement of HDL cholesterol indubitably correlates with future cardiovascular risk. Yet, the utility of therapies that raise HDL cholesterol levels in blood as effective

interventions to reduce cardiovascular vascular events has come into question. Blood HDL levels vary inversely with those of triglycerides, and the independent role of HDL versus triglycerides as a cardiovascular risk factor remains unsettled. The 2013 guideline does not advocate any specific therapy for raising HDL. Indeed, multiple recent trials failed to show that raising HDL cholesterol levels improves cardiovascular outcomes, and recent

genetic studies cast doubt on low HDL as a causal risk factor for atherosclerotic events. Weight loss and physical activity can raise HDL, and these lifestyle measures merit universal adoption. Nicotinic acid, particularly in combination with statins, can robustly raise HDL, but clinical trial data do not support the effectiveness of nicotinic acid in cardiovascular risk reduction. Agonists of nuclear receptors provide another potential avenue for raising HDL levels. Yet patients treated with peroxisome proliferator-activated receptor α and γ (PPAR- α and - γ) agonists have not consistently shown improved cardiovascular outcomes, and at least some PPAR agonists have been associated with worsened cardiovascular outcomes. Other agents in clinical development raise HDL levels by inhibiting cholesteryl ester transfer protein (CETP). Two such agents have undergone large-scale clinical evaluation and have not shown efficacy in improving cardiovascular outcomes.

119. The answer is B.

(Chap. 39) Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. In normal conditions, for any given level of a demand for oxygen, the myocardium will control the supply of oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction. The major determinants of myocardial oxygen demand (MVO_2) are heart rate, myocardial contractility, and ventricular wall tension (stress). Heart rhythm is not a major determinant of myocardial oxygen demand.

120. The answer is E.

(Chap. 39) The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. The need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate a great capacity for dilation. For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and, in this manner, regulate the supply of oxygen and substrate to the myocardium. The epicardial coronary arteries, in the normal state, provide only trivial resistance to flow. Myocardial oxygen extraction is relatively fixed. During tachycardia, the diastolic time period is shortened relative to the systolic period.

121. The answer is B.

(Chap. 39) A wide range of abnormalities in cell metabolism, function, and structure underlie these mechanical disturbances during ischemia. The normal myocardium metabolizes fatty acids and glucose to carbon dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is converted to lactate; intracellular pH is reduced, as are the myocardial stores of

high-energy phosphates (i.e., adenosine triphosphate and creatine phosphate). Impaired cell membrane function leads to the leakage of potassium and the uptake of sodium by myocytes, as well as an increase in cytosolic calcium.

122. The answer is E.

(Chap. 39) Angina pain can arise in or radiate to the back, interscapular region, root of the neck, jaw, teeth, and epigastrium. Angina is rarely localized below the umbilicus or above the mandible. A useful finding in assessing a patient with chest discomfort is the fact that myocardial ischemic discomfort does not radiate to the trapezius muscles; that radiation pattern is more typical of pericarditis.

123. The answer is B.

(Chap. 39) Many patients report a fixed threshold for angina, which occurs predictably at a certain level of activity, such as climbing two flights of stairs at a normal pace. In these patients, coronary stenosis and myocardial oxygen supply are fixed, and ischemia is precipitated by an increase in myocardial oxygen demand; they are said to have stable exertional angina. Angina can be classified by the Canadian Cardiovascular Society Functional Class as shown in Table 5.

124. The answer is C.

(Chap. 39) The ECG exercise stress test is used to discover any limitation in exercise performance, detect typical ECG signs of myocardial ischemia, and establish their relationship to chest discomfort. The ischemic ST-segment response generally is defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 seconds (Figure 28). Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Although T-wave abnormalities, conduction disturbances, and ventricular arrhythmias that develop during exercise should be noted, they are also not diagnostic. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate [MPHR] for age and sex) is not achieved are considered nondiagnostic. This patient did not achieve 85% MPHR ($220 - \text{age} = \text{MPHR}$), and the ST-segment changes are described as upsloping. Finally, blood pressure increase is a normal response to exercise.

125. The answer is C.

(Chap. 40) Non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) is most commonly caused by an imbalance between oxygen supply and oxygen demand resulting from a partially occluding thrombus forming on a disrupted atherothrombotic coronary plaque or on eroded coronary artery endothelium. Severe ischemia or myocardial necrosis may occur consequent to the reduction of coronary blood flow caused by the thrombus and by downstream embolization of platelet aggregates and/or

TABLE 5 Cardiovascular Disease Classification Chart

	New York Heart Association	Canadian Cardiovascular Society
Class	Functional Classification	Functional Classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina present with strenuous or rapid or prolonged exertion at work or recreation.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions.
IV	Patients have cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to perform any physical activity without discomfort—anginal syndrome may be present at rest.

Source: Modified from L Goldman et al: Circulation 64:1227, 1981.

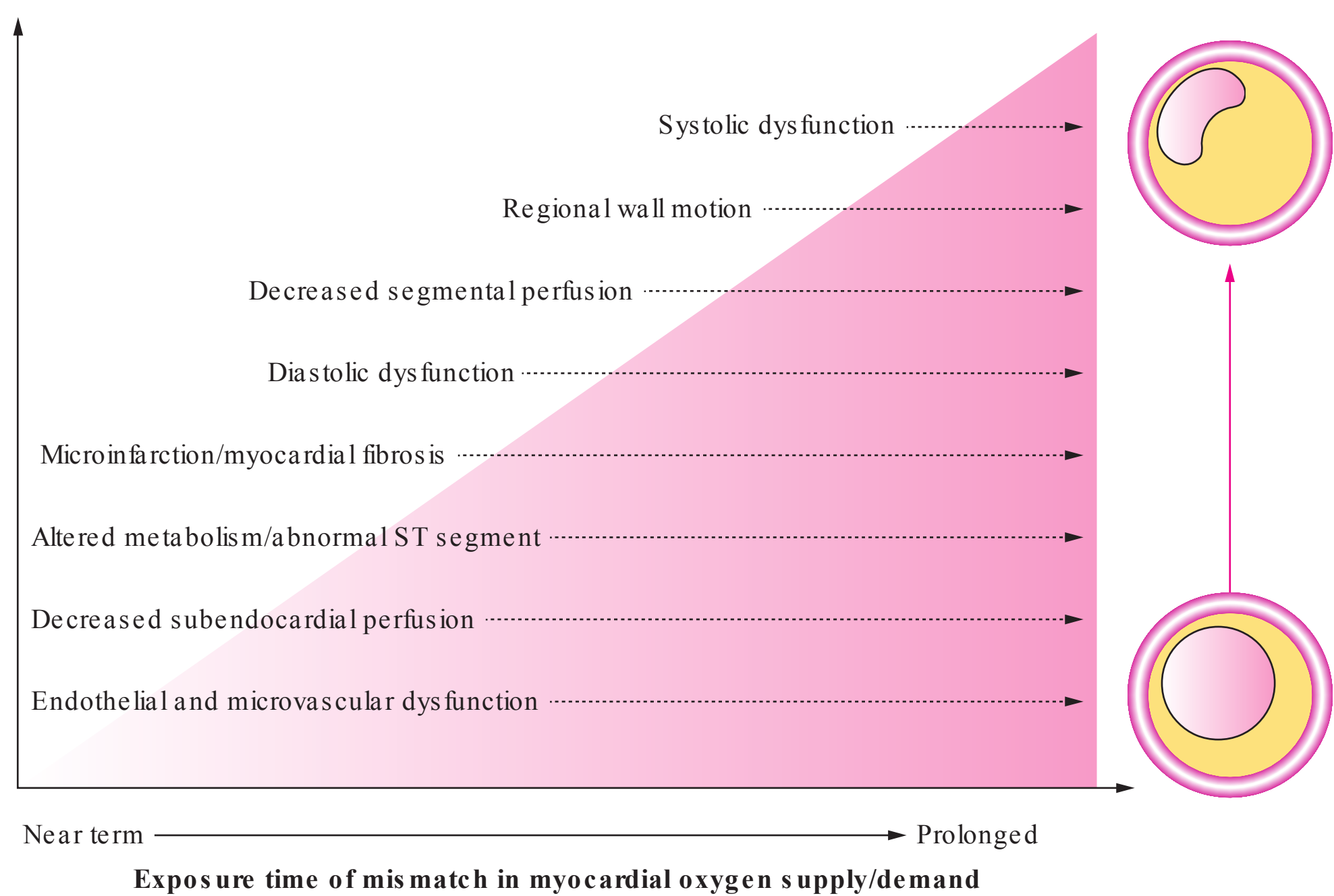


FIGURE 28 Modified from LJ Shaw et al: J Am Coll Cardiol 54:1561, 2009. Original figure illustration by Rob Flewell.

atherosclerotic debris. Other causes of NSTEMI-ACS include: (1) dynamic obstruction (e.g., coronary spasm, as in Prinzmetal variant angina); (2) severe mechanical obstruction due to progressive coronary atherosclerosis; and (3) increased myocardial oxygen demand produced by conditions such as fever, tachycardia, and thyrotoxicosis in the presence of fixed epicardial coronary obstruction. More than one of these processes may be involved. Although microvascular endothelial dysfunction can cause angina, it is not thought to be a cause of myocardial infarction.

126. The answer is E.

(Chap. 40) The diagnosis of acute coronary syndrome (ACS) is based largely on the clinical presentation. Typically, chest discomfort is severe and has at least one of three features: (1) it occurs at rest (or with minimal exertion), lasting >10 minutes; (2) it is of relatively recent onset (i.e., within the prior 2 weeks); and/or (3) it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previous episodes). The diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI) is established if a patient with these clinical features develops evidence of myocardial necrosis, as reflected in abnormally elevated levels of biomarkers of cardiac necrosis. Given the ECG without ST elevations, this patient does not have ST-segment elevation myocardial infarction (STEMI). Also, this clinical presentation of accelerating angina now occurring at rest obviates stable angina. However, because this patient does not yet have cardiac biomarker results, one cannot differentiate between unstable angina and NSTEMI. Further information is needed.

127. The answer is E.

(Chap. 40) It is important to remember that although cardiac troponin biomarkers (troponin I or T) are quite sensitive for myocardial infarction due to coronary occlusion, they lack somewhat in specificity. In patients without a clear clinical history of myocardial ischemia, minor cardiac troponin elevations have been reported and can be caused by congestive heart failure, myocarditis, or pulmonary embolism; in addition, using high-sensitivity assays, they may occur in ostensibly normal subjects. Thus, in patients with an unclear history, small elevations of cardiac troponin, especially if they are persistent, may not be diagnostic of an ACS. In this patient, the troponin elevation is likely due to his hypertensive urgency brought on by missed hemodialysis and volume overload. Treating the proximal cause will help him. It would be prudent to continue to trend cardiac biomarkers and ECGs over time as well.

128. The answer is E.

(Chap. 40) This patient is suffering from an NSTEMI. The two cornerstones of pharmacologic therapy in NSTEMI management are reduction of myocardial oxygen demand and antithrombotic therapy targeted at a presumed partially occluding thrombus forming on disrupted

atherothrombotic coronary plaque. Aspirin in combination with a P2Y₁₂ receptor blocker (e.g., clopidogrel, ticagrelor, or prasugrel) is an appropriate antiplatelet option, and options for anticoagulants include: (1) unfractionated heparin (UFH), long the mainstay of therapy; (2) the low-molecular-weight heparin (LMWH) enoxaparin, which has been shown to be superior to UFH in reducing recurrent cardiac events, especially in patients managed by a conservative strategy but with some increase in bleeding; (3) bivalirudin, a direct thrombin inhibitor that is similar in efficacy to either UFH or LMWH but causes less bleeding and is used just prior to and/or during percutaneous coronary intervention; and (4) the indirect factor Xa inhibitor fondaparinux, which is equivalent in efficacy to enoxaparin but appears to have a lower risk of major bleeding. To reduce myocardial oxygen demand, β -blockade administration targeting a heart rate of 60 bpm is reasonable, although it should be used with caution or avoided in the presence of heart failure (not present in this patient). Likewise, nitroglycerin is a commonly used and effective antianginal therapy. However, a direct contraindication is the use of phosphodiesterase inhibitors (such as tadalafil in this patient), and coadministration can result in catastrophic hypotension.

129. The answer is A.

(Chap. 41) This patient is presenting with classic ischemic chest pain by history. When present in such a classic manner, it is unmistakable. After obtaining this history, the clinical working diagnosis is ACS. The next most important step in the decision tree is to determine whether the patient is having an STEMI or non-ST-segment elevation ACS (NSTEMI or unstable angina). This can only be accomplished by the ECG. Serum biomarkers (troponin and creatine kinase [CK]-MB) take minutes to hours to return and may not be elevated in the initial several hours of an infarction. In practical terms, the high-sensitivity troponin assays are of less immediate value in patients with STEMI. Contemporary urgent reperfusion strategies necessitate making a decision (based largely on a combination of clinical and ECG findings) before the results of blood tests have returned from the laboratory. Although echocardiogram may demonstrate wall motion abnormalities in areas of ischemia, it cannot differentiate between ST-segment elevation and non-ST-segment elevation ACS. Coronary CT angiography is not warranted in a patient having active ischemic pain. Figure 29 provides a flow chart of the decision tree facing the clinician treating a patient with ischemic discomfort.

130. The answer is E.

(Chap. 41) Cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI) have different amino acid sequences from those of the skeletal muscle forms of these proteins. These differences permitted the development of quantitative assays for cTnT and cTnI with highly specific

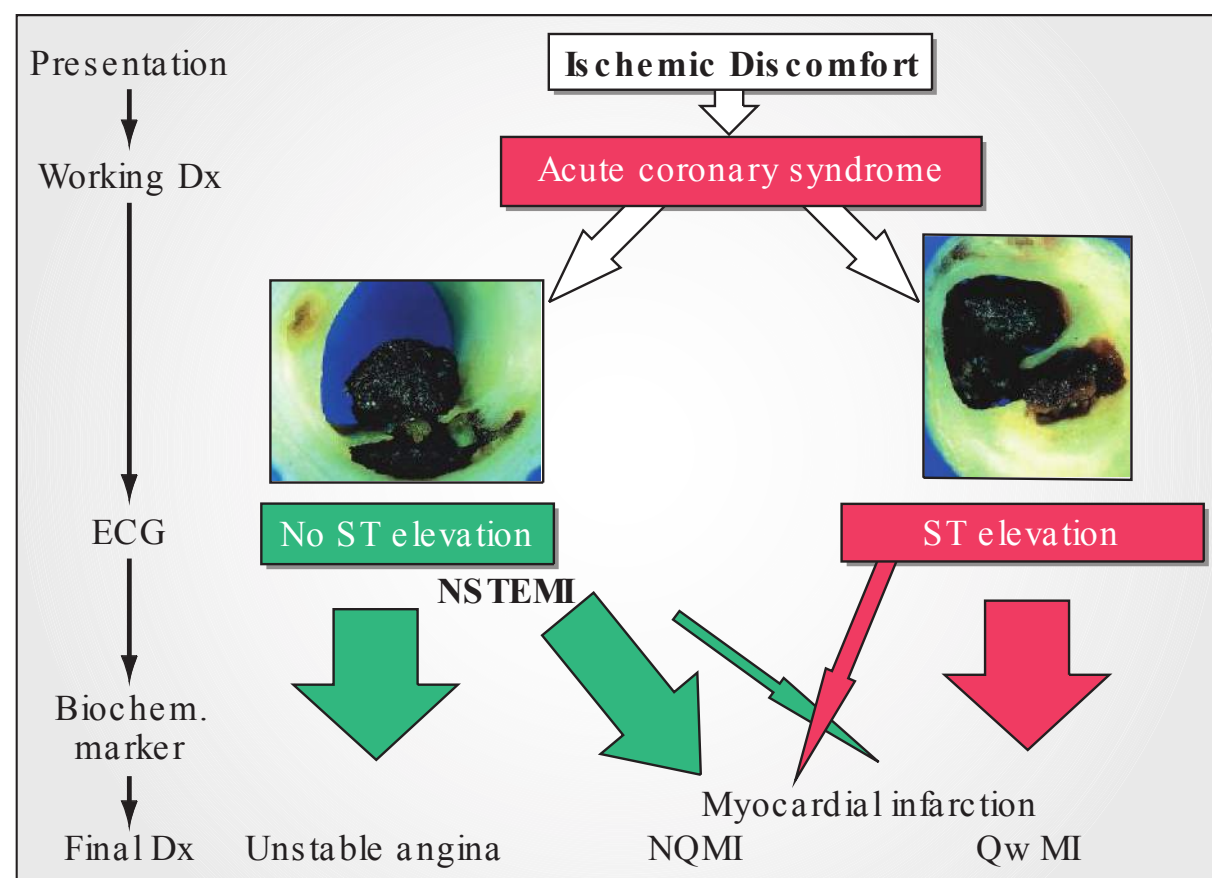


FIGURE 29 Dx, diagnosis; ECG, electrocardiogram; NQMI, non-Q-wave myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; Qw MI, Q-wave myocardial infarction. Adapted from CW Hamm et al: *Lancet* 358:1533, 2001, and MJ Davies: *Heart* 83:361, 2000; with permission from the BMJ Publishing Group.

monoclonal antibodies. Because cTnT and cTnI are not normally detectable in the blood of healthy individuals but may increase after STEMI to levels many times higher than the upper reference limit (the highest value seen in 99% of a reference population not suffering from MI), the measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI. An important drawback of total creatine kinase (CK) measurement is its lack of specificity for STEMI, as CK may be elevated with skeletal muscle disease or trauma, including intramuscular injection. The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentrations in extracardiac tissue and, therefore, is considerably more specific. However, cardiac surgery, myocarditis, and electrical cardioversion often result in elevated serum levels of the MB isoenzyme. The nonspecific reaction to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain and persists for 3–7 days; the white blood cell count often reaches levels of 12,000–15,000/ μL . The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks. Similarly, the lactate dehydrogenase may rise in the setting of acute MI but is nonspecific.

131. The answer is C.

(Chap. 41) CK rises within 4–8 hours and generally returns to normal by 48–72 hours. The cardiac troponin assays have a similar time frame for rise, but generally last much longer (7–10 days after STEMI). Early reperfusion will cause an earlier peak of biomarker measurements (See Figure 30.)

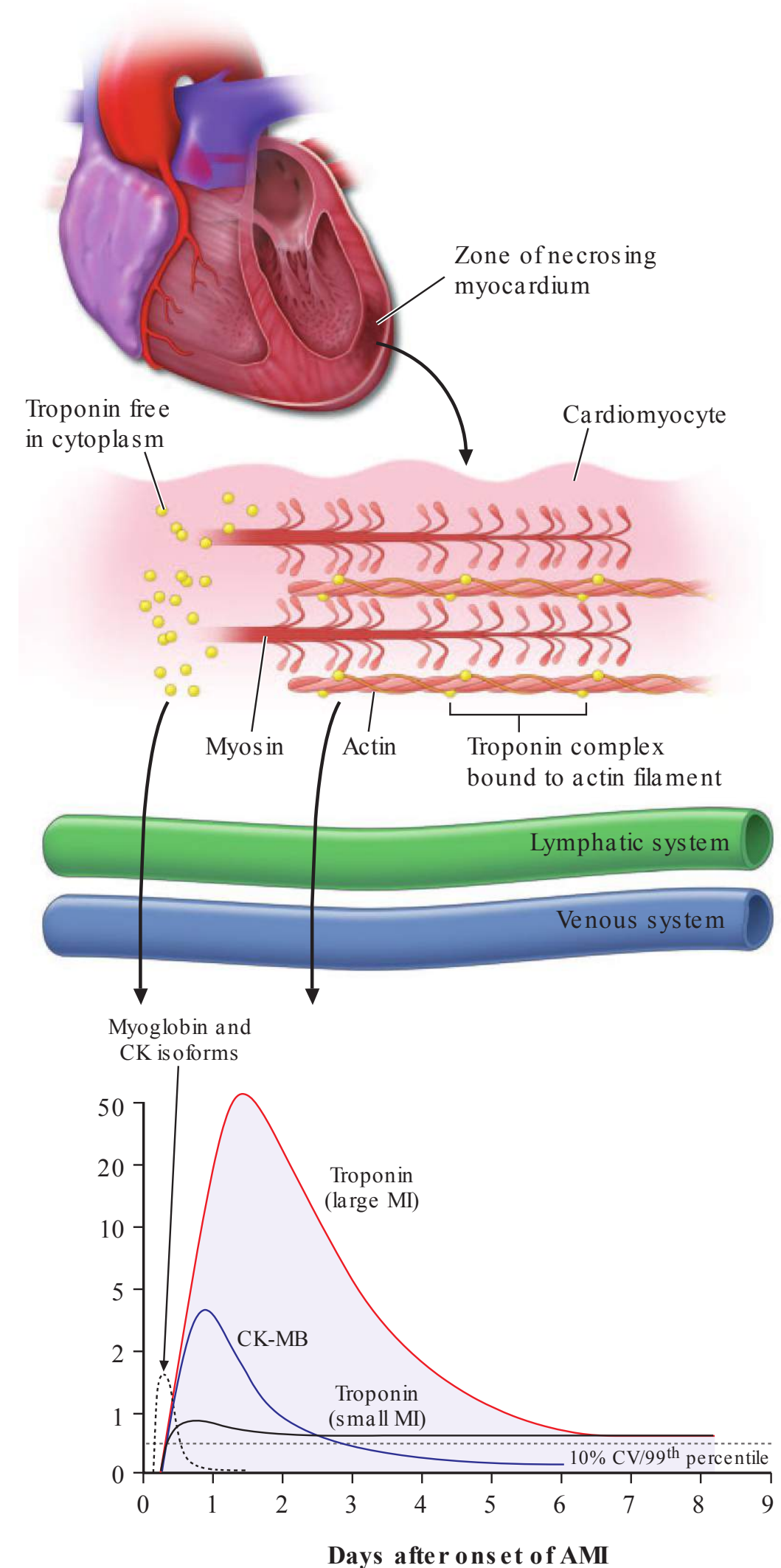


FIGURE 30 AMI, acute myocardial infarction; CK, creatine kinase; MI, myocardial infarction. Modified from EM Antman: *Decision making with cardiac troponin tests*. *N Engl J Med* 346:2079, 2002 and AS Jaffe, L Babuin, FS Apple: *Biomarkers in acute cardiac disease: The present and the future*. *J Am Coll Cardiol* 48:1, 2006.

132. The answer is A.

(Chap. 41) Most out-of-hospital deaths from STEMI are due to the sudden development of ventricular fibrillation. The vast majority of deaths due to ventricular fibrillation occur within the first 24 hours of the onset of symptoms, and of these, over half occur in the first hour. Therefore, the major elements of prehospital care of patients with suspected STEMI include: (1) recognition of symptoms by the patient and prompt seeking of medical attention; (2) rapid deployment of an emergency medical team capable of performing resuscitative

maneuvers, including defibrillation; (3) expeditious transportation of the patient to a hospital facility that is continuously staffed by physicians and nurses skilled in managing arrhythmias and providing advanced cardiac life support; and (4) expeditious implementation of reperfusion therapy. The greatest delay usually occurs not during transportation to the hospital but, rather, between the onset of pain and the patient's decision to call for help. This delay can best be reduced by healthcare professionals educating the public concerning the significance of chest discomfort and the importance of seeking early medical attention. Regular office visits with patients who have a history of or are at risk for ischemic heart disease are important "teachable moments" for clinicians to review the symptoms of STEMI and the appropriate action plan.

133. The answer is E.

(Chap. 41) All of these choices are appropriate therapy for patients with STEMI in certain situations. Aspirin is an irreversible cyclooxygenase inhibitor and thus inhibits the production of thromboxane A₂. β -Blockers reduce myocardial oxygen demand by reducing cardiac chronotropy and inotropy. They should be used with caution in patients with myocardial infarction and any signs of delayed conduction (prolonged PR interval), heart failure, or risk for cardiogenic shock. Clopidogrel inhibits the P2Y₁₂ adenosine diphosphate platelet receptor to inhibit platelet aggregation. Abciximab and eptifibatide are glycoprotein IIb/IIIa inhibitors that also inhibit platelet aggregation. Although nitroglycerin is effective for antianginal effects in the setting of STEMI, it enacts those effects through decreasing preload and perhaps through some direct nitric oxide-induced coronary vasodilation. Nitroglycerin has minimal effect on systemic afterload.

134. The answer is D.

(Chap. 41) This patient has evidence of failure of reperfusion with fibrinolytic therapy (persistent chest pain and ST-segment elevation >90 minutes). In this case, rescue percutaneous coronary intervention (PCI) should be pursued. Repeating a second dose of tissue plasminogen activator or a different fibrinolytic is not warranted and potentially dangerous. Coronary artery bypass grafting is not warranted prior to knowing the anatomy, and in the immediate setting after administration of fibrinolytics, it carries an exceedingly high risk of serious hemorrhage.

135. The answer is E.

(Chap. 41) This patient has an accelerated idioventricular rhythm, a common finding in patients with successful reperfusion after thrombolytic therapy. This rhythm is benign and requires no further therapy. It invariably resolves on its own. Flecainide (a class I antiarrhythmic) is contraindicated in post-MI patients because it was found to increase mortality in the CAST trial. Amiodarone or metoprolol would be appropriate therapy if this

was ventricular tachycardia or perhaps supraventricular tachycardia. Carotid sinus massage would be appropriate in the setting of supraventricular tachycardia.

136. The answer is D.

(Chap. 42) Percutaneous therapy of coronary artery disease underwent a paradigm shift with the introduction of coronary stents in 1994. However, metallic stents are also prone to stent thrombosis (1%–3%), either acute (<24 hours) or subacute (1–30 days), which can be ameliorated by greater attention to full initial stent deployment and the use of dual antiplatelet therapy (DAPT) (aspirin plus a platelet P2Y₁₂ receptor blocker [clopidogrel, prasugrel, or ticagrelor]). Late (30 days–1 year) and very late (>1 year) stent thromboses occur infrequently with stents but are slightly more common with first-generation drug-eluting stents, generally necessitating DAPT for 1 year or longer. Use of the second-generation stents (such as the everolimus-eluting stent) is associated with lower rates of late and very late stent thromboses, and shorter durations of DAPT may be possible. Premature discontinuation of DAPT, particularly in the first month after implantation, is associated with a significantly increased risk for stent thrombosis (three- to nine-fold greater). Stent thrombosis results in death in 10%–20% of patients and myocardial infarction in 30%–70% of patients. Elective surgery (such as cataract removal) that requires discontinuation of antiplatelet therapy after drug-eluting stent implantation should be postponed until after 6 months and preferably after 1 year, if at all possible. At that point, clopidogrel can be reasonably discontinued if no other mitigating factors are present. If at all possible, aspirin should be continued.

137. The answer is D.

(Chap. 42) The lines between coronary artery bypass grafting (CABG) and PCI for revascularization of CAD have been shifting for the better part of two decades. As PCI technique and technology improve, it has become the dominant form of revascularization and is performed now more than twice as often as CABG. However, there remain select patients in whom CABG and PCI either exist in therapeutic equipoise or CABG is clearly a superior option. One such population is patients with multivessel disease. When revascularization is indicated, the choice of PCI or CABG depends on a number of clinical and anatomic factors. The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial compared PCI with the paclitaxel drug-eluting stent to CABG in 1800 patients with three-vessel coronary disease or left main disease. The study found no difference in death or myocardial infarction at 1 year (options A and E), but repeat revascularization was significantly higher in the stent-treated group (13.5% vs. 5.9%) (option B), whereas stroke was significantly higher in the surgical group (2.2% vs. 0.6%) (option C). The combined primary end point of death, myocardial

infarction, stroke, or revascularization was significantly better with CABG, particularly in those with the most extensive CAD. The 3-year results confirm these findings. The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 patients with diabetes and multivessel disease and showed a significantly lower primary end point of death, myocardial infarction, or stroke with CABG than PCI. These studies support CABG for those with the most severe left main and three-vessel disease or those with diabetes. Lesser degrees of multivessel disease in patients with or without diabetes have an equal outcome with PCI. The choice of PCI versus CABG is also related to the anticipated procedural success and complications of PCI and the risks of CABG (option D). For PCI, the characteristics of the coronary anatomy are critically important. The location of the lesion in the vessel (proximal or distal), the degree of tortuosity, and the size of the vessel are considered. In addition, the lesion characteristics, including the degree of the stenosis, the presence of calcium, lesion length, and presence of thrombus, are assessed.

138. The answer is B.

(Chap. 42) Chronic total occlusions (CTOs) represent one of the greatest therapeutic challenges in interventional cardiology. Proper patient and lesion selection and meticulous technique are required to successfully and safely perform PCI on a CTO. In asymptomatic high-risk patients or lesions, it is recommended to forego PCI attempts at CTO given the elevated risk profile of the procedure. However, in this symptomatic patient with a high-risk stress test, an attempt at PCI is reasonable. Incomplete revascularization due to an untreated CTO is associated with an increased mortality rate (hazard ratio = 1.36; 95% confidence interval [CI], 1.12–1.66, $p < .05$). Successful PCI of a CTO leads to a 3.8%–8.4% absolute reduction in mortality, symptom relief, and improved left ventricular function. Newer techniques, such as the retrograde approach to crossing total occlusions, are useful when the antegrade approach fails or is not feasible and there are well-developed collateral vessels.

139. The answer is B.

(Chap. 53) Saphenous vein grafts have a failure rate of up to 20% after 1 year and as high as 50% by 5 years. This is much higher than the failure rate of arterial conduits (e.g., left internal mammary arteries) (option D). Venous graft failure (after >1 month) results from intimal hyperplasia and atherosclerosis, rarely from embolization (option A). Saphenous vein graft PCI is associated with distal embolization of atherosclerotic debris and microthrombi leading to microvascular occlusion, reduced antegrade blood flow (the “no-reflow” phenomenon), and myocardial infarction. Although the risk of no reflow is higher in saphenous vein graft PCI than in native-vessel PCI (option D),

the benefit of successful revascularization and the ability to reduce the risk with a distal protection device often warrants proceeding with PCI (option C). Embolic distal protection devices decrease the risk of distal embolization, as well as the incidence of no reflow and myocardial infarction associated with saphenous vein graft interventions (option B).

140. The answer is E.

(Chap. 53) This patient has classic findings for aortic stenosis (AS) including a late-peaking systolic murmur, pulsus parvus et tardus, and symptoms of angina and heart failure. Although some medications may reduce symptoms (e.g., diuretics for heart failure symptoms), severe AS has historically been a surgical disease; medications have no role in reducing mortality. Mortality from severe AS is high, with 1- and 5-year survival rates for nonsurgical candidates of 62% and 38%, respectively. Although percutaneous balloon valvotomy can be used for the acutely ill or “crashing” patient with severe AS, short-term complication rates are high (approximated at 10%–20%), valve area rarely exceeds 1 cm^2 after balloon valvotomy, most patients return to their preprocedure valve area by 6–12 months, and the procedure does not affect mortality risk. Previously, nonsurgical candidates were advised to pursue comfort measures, sometimes including hospice care. However, with the advent of transcatheter aortic valve replacement (TAVR), we are now able to offer a viable treatment option to many patients who are too high risk for surgical aortic valve replacement. TAVR has been shown to be superior to usual care in very high risk patients. Mrs. Edwards will have to undergo further testing to ensure that her anatomy is amenable to TAVR, but it remains a viable treatment option for this very ill woman.

141. The answer is B.

(Chap. 43) Hypertension is present in all populations except for a small number of individuals living in developing countries. In industrialized societies, blood pressure increases steadily during the first two decades of life. In children and adolescents, blood pressure is associated with growth and maturation. Blood pressure “tracks” over time in children and between adolescence and young adulthood. In the United States, average systolic blood pressure is higher for men than for women during early adulthood, although among older individuals, the age-related rate of rise is steeper for women. Consequently, among individuals age 60 and older, systolic blood pressures of women are higher than those of men. Among adults, diastolic blood pressure also increases progressively with age until the age of 55 years, after which it tends to decrease. The consequence is a widening of pulse pressure (the difference between systolic and diastolic blood pressure) beyond age 60. In the United States, based on results of the National Health and Nutrition Examination Survey (NHANES),

approximately 30% (age-adjusted prevalence) of adults, or at least 65 million individuals, have hypertension (defined as any one of the following: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or taking antihypertensive medications). Hypertension prevalence is 33.5% in non-Hispanic blacks, 28.9% in non-Hispanic whites, and 20.7% in Mexican Americans.

142. The answer is B.

(Chap. 43) Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias. Stroke is the second most frequent cause of death in the world; it accounts for 5 million deaths each year, with an additional 15 million persons having nonfatal strokes. Elevated blood pressure is the strongest risk factor for stroke. Renal disease is both a common effect and cause of hypertension but is not as common a cause of mortality as cardiac disease in hypertensive patients. Lung or liver dysfunction is a rarer cause of mortality in hypertensive patients.

143 and 144. The answers are D and E, respectively.

(Chap. 43) This patient presents at a young age with hypertension that is difficult to control, raising the question of secondary causes of hypertension. The most likely diagnosis in this patient is primary hyperaldosteronism, also known as Conn syndrome. The patient has no physical features that suggest congenital adrenal hyperplasia or Cushing syndrome. In addition, there is no glucose intolerance as is commonly seen in Cushing syndrome. The lack of episodic symptoms and the labile hypertension make pheochromocytoma unlikely. The findings of hypokalemia and metabolic alkalosis in the presence of difficult-to-control hypertension yield the likely diagnosis of Conn syndrome. Diagnosis of the disease can be difficult, but the preferred test is the plasma aldosterone/renin ratio. This test should be performed at 8:00 AM, and a ratio above 30–50 is diagnostic of primary hyperaldosteronism. Caution should be made in interpreting this test while the patient is on ACE inhibitor therapy because ACE inhibitors can falsely elevate plasma renin activity. However, a plasma renin level that is undetectable or an elevated aldosterone/renin ratio in the presence of ACE inhibitor therapy is highly suggestive of primary hyperaldosteronism. Selective adrenal vein renin sampling may be performed after the diagnosis to help determine if the process is unilateral or bilateral. Although fibromuscular dysplasia is a common secondary cause of hypertension in young females, the presence of hypokalemia and metabolic alkalosis should suggest Conn syndrome. Thus, magnetic resonance imaging of the renal arteries is unnecessary in this case. Measurement of 24-hour urine

collection for potassium wasting and aldosterone secretion can be useful in the diagnosis of Conn syndrome. The measurement of metanephrines or cortisol is not indicated.

145. The answer is C.

(Chap. 43) This patient is suffering from hypertensive emergency, specifically malignant hypertension. Hallmarked by rapid arterial changes and loss of cerebral autoregulation, the clinical signs include very high blood pressure, delirium due to cerebral hyperperfusion, renal failure with proteinuria and hematuria, and hemolytic anemia. Mortality in the first several hours is high with this disease state, and rapid treatment is warranted. However, most patients presenting with malignant hypertension also have longstanding chronic elevations in blood pressure and a change in the “set point” of the cerebral autoregulation. Reducing the blood pressure rapidly to normal levels for the regular population often leads to hypoperfusion and can lead to watershed cerebral infarcts. In the setting of hypertensive emergency, a reduction of mean arterial pressure in minutes to hours by 25% is recommended. Parenteral therapy has a more rapid onset and is much more easily titrated than oral therapy, which is inappropriate in the emergent setting. Immediate-release nifedipine is particularly potent and is associated with a higher risk of myocardial infarction when used in this setting. Plasmapheresis would be warranted if this were a case of thrombotic thrombocytopenic purpura (TTP), but with the normal platelets count in this case, it is unlikely TTP.

146. The answer is D.

(Chap. 44) Rates of urinary albumin excretion (UAE) are predictive of systemic atherosclerotic disease events. Increased UAE may develop years before cardiovascular events. The renal vasculature is unusually complex with rich arteriolar flow to the cortex in excess of metabolic requirements, consistent with its primary function as a filtering organ. After delivering blood to cortical glomeruli, the postglomerular circulation supplies deeper medullary segments that support energy-dependent solute transport at multiple levels of the renal tubule. These postglomerular vessels carry less blood, and high oxygen consumption leaves the deeper medullary regions at the margin of hypoxemia. Thus, the venous blood from the medulla typically has much lower oxygen saturation than cortical venous blood. The glomerular capillary endothelium shares susceptibility to oxidative stress, pressure injury, and inflammation with other vascular territories.

147. The answer is B.

(Chap. 44) Renal artery stenosis is common and often has only minor hemodynamic effects. The earliest finding may be an elevated systemic renin level. Fibromuscular dysplasia (FMD) is reported in 3%–5% of normal

subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but sometimes produces total occlusion and can be associated with renal artery aneurysms. Critical levels of stenosis lead to a reduction in perfusion pressure that activates the renin-angiotensin system, reduces sodium excretion, and activates sympathetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages, widely varying pressures, loss of circadian blood pressure rhythms, and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. Elevated renal artery velocities by Doppler ultrasound above 200 cm/s generally predict hemodynamically important lesions (>60% vessel lumen occlusion). Although renin levels and activity are elevated in the state of significant renal artery stenosis, the relative level does not predict response to therapy.

148. The answer is B.

(Chap. 44) This patient's clinical scenario is most consistent with atheroembolic renal disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinical cases can be linked to precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy, or trauma. Clinical manifestations of this syndrome commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss, are present in less than half of patients, although cutaneous manifestations including livedo reticularis and localized toe gangrene may be more common. Worsening hypertension and deteriorating kidney function are common. Typical laboratory findings include rising creatinine, transient eosinophilia (60%–80% of cases), elevated erythrocyte sedimentation rate (ESR), and hypocomplementemia (15% of cases). Contrast-induced nephropathy is not associated with fever, high ESR, eosinophilia, or livedo reticularis of the lower extremities. It would be unusual to develop interstitial nephritis without exposure to a new medication, and other than eosinophilia, the laboratory abnormalities are not supportive in this case. Likewise, the sudden development of hypereosinophilic syndrome in a 75-year-old man would be highly unlikely. Finally, although Churg-Strauss syndrome is a small- to medium-vessel vasculitis associated with renal dysfunction and eosinophilia, almost all patients experience atopy and asthma-like lung disease, which are absent in this patient.

149. The answer is B.

(Chap. 45) The D-dimer measured by enzyme-linked immunosorbent assay (ELISA) is elevated in the setting of breakdown of fibrin by plasmin, and the presence of a positive D-dimer can prompt the need for additional imaging for deep venous thrombosis and/or pulmonary embolus in specific clinical situations where the patient would be considered to have an elevation in D-dimer. However, one must be cautious about placing value on an elevated D-dimer in other situations where there can be an alternative explanation for the elevated level. Of the scenarios listed in the question, the only patient who would be expected to have a negative D-dimer would be the patient with calf pain and recent air travel. The presence of a normal alveolar-arterial oxygen gradient cannot reliably differentiate between those with and without pulmonary embolism. In all the other scenarios, elevations in D-dimer could be related to other medical conditions and provide no diagnostic information to inform the clinician regarding the need for further evaluation. Some common clinical situations in which the D-dimer is elevated include sepsis, myocardial infarction, cancer, pneumonia, the postoperative state, and the second and third trimesters of pregnancy.

150. The answer is E.

(Chap. 45) Warfarin should not be used alone as initial therapy for the treatment of venous thromboembolic disease (VTE) for two reasons. First, warfarin does not achieve full anticoagulation for at least 5 days as its mechanism of action is to decrease the production of vitamin K–dependent coagulation factors in the liver. Second, a paradoxical reaction that promotes coagulation may also occur upon initiation of warfarin as it also decreases the production of the vitamin K–dependent anticoagulants protein C and protein S, which have shorter half-lives than the procoagulant factors. For many years, unfractionated heparin delivered IV was the treatment of choice for VTE. However, it requires frequent monitoring of activated partial thromboplastin time levels and hospitalization until the therapeutic international normalized ratio is achieved with warfarin. There are now several safe and effective alternatives to unfractionated heparin that can be delivered subcutaneously. Low-molecular-weight heparins (LMWHs; enoxaparin, tinzaparin) are fragments of unfractionated heparin with a lower molecular weight. These compounds have a greater bioavailability, longer half-life, and more predictable onset of action. Their use in renal insufficiency should be considered with caution because LMWHs are renally cleared. Fondaparinux is a direct factor Xa inhibitor that, like LMWHs, requires no monitoring of anticoagulant effects and has been demonstrated to be safe and effective in treating both deep venous thrombosis and pulmonary embolism.

151. The answer is C.

(Chap. 45) Many patients with pulmonary embolism (PE) have no evidence of deep venous thrombosis because the clot has already embolized to the lungs. The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial O_2 tension gradient, which represents the inefficiency of O_2 transfer across the lungs. Physiologic dead space increases because ventilation to gas exchange units exceeds blood flow through the pulmonary capillaries. Other pathophysiologic abnormalities include: (1) increased pulmonary vascular resistance due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents, such as serotonin; release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial O_2 gradient; (2) impaired gas exchange due to increased alveolar dead space from vascular obstruction, hypoxemia from ventilation-perfusion mismatching, right-to-left shunting, or impaired carbon monoxide diffusion capacity due to loss of gas exchange surface; (3) alveolar hyperventilation due to reflex stimulation of irritant receptors; (4) increased airway resistance due to mediator-induced bronchoconstriction; and (5) decreased pulmonary compliance due to lung edema, lung hemorrhage, or loss of surfactant. In the setting of acute pulmonary embolism, pulmonary vascular resistance and thus RV pressures acutely rise. Hypotension in this setting is due to acute RV failure. The left ventricle is often contracting in a hyperdynamic fashion due to a catecholamine surge and compression from the dilated, failing RV.

152. The answer is A.

(Chap. 45) In patients with PE, the two principal indications for insertion of an inferior vena cava filter are (1) active bleeding that precludes anticoagulation and (2) recurrent venous thrombosis despite intensive anticoagulation. Prevention of recurrent PE in patients with right heart failure who are not candidates for fibrinolysis and prophylaxis of extremely high-risk patients are “softer” indications for filter placement. The filter itself may fail by permitting the passage of small- to medium-size clots. Large thrombi may embolize to the pulmonary arteries via collateral veins that develop. A more common complication is caval thrombosis with marked bilateral leg swelling. Paradoxically, by providing a nidus for clot formation, filters increase the deep venous thrombosis rate, even though they usually prevent PE (over the short term). Retrieval filters can now be placed for patients with an anticipated temporary bleeding disorder or for patients at temporary high risk of PE, such as individuals undergoing bariatric surgery who have a prior history of perioperative PE. The filters can be retrieved up to several months after insertion unless thrombus forms and is trapped within the filter. The retrievable filter becomes

permanent if it remains in place or if, for technical reasons such as rapid endothelialization, it cannot be removed.

153. The answer is C.

(Chap. 45) This patient is suffering from massive PE as a complication of her bariatric surgery. Rather than being defined by the absolute size of clot burden of PE on imaging, massive PE is defined by the presence of hypotension due to the embolism. Usually, one would consider emergent thrombolysis (either systemic or catheter directed) for a patient with massive PE, but Ms. Tupulo has just completed a large open abdominal operation, which is a direct contraindication for thrombolytics, such as tissue plasminogen activator or urokinase, because she would be at very high risk for life-threatening hemorrhage. In this case, the goal is to alleviate right heart obstruction as soon and effectively as possible. Emergent surgical pulmonary embolectomy provides this and should be pursued before the onset of multisystem organ failure renders the surgery too high risk. Inferior vena cava filter placement could be pursued later if it is discovered that the patient has residual lower extremity thrombus. Although systemic anticoagulation will be needed after embolectomy, enoxaparin represents a poor choice given the patient's very high body weight and the only partially reversible nature of LMWHs, a consideration given the patient's high risk of bleeding.

154. The answer is A.

(Chap. 46) An aneurysm is defined as a pathologic dilation of a segment of a blood vessel. A true aneurysm involves all three layers of the vessel wall and is distinguished from a pseudoaneurysm, in which the intimal and medial layers are disrupted and the dilated segment of the aorta is lined usually by adventitia only and, at times, by perivascular clot. Aneurysms also may be classified according to their gross appearance. A fusiform aneurysm affects the entire circumference of a segment of the vessel, resulting in a diffusely dilated artery. In contrast, a saccular aneurysm involves only a portion of the circumference, resulting in an outpouching of the vessel wall.

155. The answer is C.

(Chap. 46) Factors associated with degenerative aortic aneurysms include aging, cigarette smoking, hypercholesterolemia, hypertension, and male sex.

156. The answer is D.

(Chap. 46) This patient has a classical phenotype for Loeys-Dietz syndrome. Loeys-Dietz syndrome is caused by mutations in the genes that encode transforming growth factor (TGF)- β receptors 1 (TGFB1) and 2 (TGFB2). Increased signaling by TGF- β and mutations of TGFB1 and TGFB2 may cause thoracic aortic aneurysms. Mutations of the gene that encodes fibrillin-1 are present in patients with Marfan syndrome. Fibrillin-1 is an important component of extracellular microfibrils,

which support the architecture of elastic fibers and other connective tissue. Deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by TGF- β . Mutations of type III procollagen have been implicated in Ehlers-Danlos type IV syndrome. Mutations of SMAD3, which encodes a downstream signaling protein involved with TGF binding to its receptors, have been described in a syndrome of thoracic aortic aneurysm; craniofacial, skeletal, and cutaneous anomalies; and osteoarthritis. Mutations of the genes encoding the smooth muscle-specific alpha-actin (ACTA2), smooth muscle cell-specific myosin heavy chain 11 (MHC11), and myosin light chain kinase (MYLK) and mutations of *TGFBR2* and *SMAD3* have been reported in some patients with nonsyndromic familial thoracic aortic aneurysms.

157. The answer is A.

(Chap. 46) For all patients with aortic dissection or hematoma, appropriate management includes reduction of shear stress with β -blockade and management of systemic hypertension to reduce tension on the dissection. However, emergent or urgent surgical therapy is indicated in patients with ascending aortic dissection and intramural hematomas (type A) and for complicated type B dissections (distal aorta). Complications that would warrant surgical intervention include propagation despite medical therapy, compromise of major branches, impending rupture, or continued pain. Thus, patient A has a distal dissection without evidence of complications and is the best candidate for medical therapy.

158. The answer is D.

(Chap. 46) Aortitis and ascending aortic aneurysms are commonly caused by cystic medial necrosis and mesoaortitis that result in damage to the elastic fibers of the aortic wall with thinning and weakening. Many infectious, inflammatory, and inherited conditions have been associated with this finding, including syphilis, tuberculosis, mycotic aneurysm, Takayasu arteritis, giant cell arteritis, rheumatoid arthritis, and the spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, Behçet disease). In addition, it can be seen with the genetic disorders Marfan syndrome and Ehlers-Danlos syndrome. Aortic disease is not typical in systemic lupus erythematosus.

159. The answer is E.

(Chap. 47) Mr. Tomazelli is describing classic symptoms of claudication due to peripheral arterial disease (PAD). By far, the most common etiology of this disease is atherosclerosis, particularly in elderly patients with hypertension, diabetes mellitus, and smoking history. The history and physical examination are often sufficient to establish the diagnosis of PAD. An objective assessment of the presence and severity of disease is obtained by noninvasive techniques. Magnetic resonance angiography,

invasive catheter-based angiography, and CT angiography are not initial tests of choice but may be used to plan revascularization strategies. The initial test of choice is an ankle-brachial index (ABI). Arterial pressure can be recorded noninvasively in the legs by placement of sphygmomanometric cuffs at the ankles and the use of a Doppler device to auscultate or record blood flow from the dorsalis pedis and posterior tibial arteries. Normally, systolic blood pressure in the legs and arms is similar. Indeed, ankle pressure may be slightly higher than arm pressure due to pulse-wave amplification. Thus, the ratio of the ankle and brachial artery pressures (termed ABI) is 1.00–1.40 in normal individuals. In the presence of hemodynamically significant lower extremity stenoses, the systolic blood pressure in the leg is decreased. ABI values of 0.91–0.99 are considered “borderline,” and those <0.90 are abnormal and diagnostic of PAD. One may also consider the pulse volume contour, which is blunted in cases of PAD.

160. The answer is D.

(Chap. 47) The natural history of patients with PAD is influenced primarily by the extent of coexisting coronary artery and cerebrovascular disease. Patients with PAD have a 15%–30% 5-year mortality rate and a two- to six-fold increased risk of death from coronary heart disease. The likelihood of symptomatic progression of PAD is lower than the chance of succumbing to coronary artery disease (CAD). Approximately 75%–80% of nondiabetic patients who present with mild to moderate claudication remain symptomatically stable. Deterioration is likely to occur in the remainder, with approximately 1%–2% of the group ultimately developing critical limb ischemia each year. The anticoagulant warfarin is as effective as antiplatelet therapy in preventing adverse cardiovascular events but causes more major bleeding; therefore, it is not indicated to improve outcomes in patients with chronic PAD. Patients with claudication should be encouraged to exercise regularly and at progressively more strenuous levels. Supervised exercise training programs involving 30- to 45-minutes sessions, three to five times per week for at least 12 weeks, prolong walking distance. Patients also should be advised to walk until nearly maximum claudication discomfort occurs and then rest until the symptoms resolve before resuming ambulation. The beneficial effect of supervised exercise training on walking performance in patients with claudication often is similar to or greater than that realized after a revascularization procedure. Vasodilators as a class have not proved to be beneficial. During exercise, peripheral vasodilation occurs distal to sites of significant arterial stenoses. As a result, perfusion pressure falls, often to levels lower than that generated in the interstitial tissue by the exercising muscle. β -Adrenergic blockers do not worsen claudication and may be used to treat hypertension, especially in patients with coexistent CAD.

161. The answer is C.

(Chap. 47) The patient presents with classic signs of arterial occlusion with limb pain and physical examination showing pallor and a pulseless, cold leg. She has no risk factors for central or peripheral atherosclerotic disease; thus, an angiogram would simply confirm the diagnosis of arterial occlusion, not demonstrate her predisposing condition. In the absence of fever or systemic symptoms, vasculitis and endocarditis are unlikely sources of arterial embolization. She likely had a paradoxical embolism in the context of an atrial septal defect, which was the source of her childhood murmur. Because many of these patients develop pulmonary hypertension with time, she is now at risk for a paradoxical embolism. Although in this context, arterial emboli frequently originate from venous thrombus, the thrombi cannot produce a paradoxical embolism in the absence of right-to-left shunt, such as in a large patent foramen ovale or an atrial septal defect, which can be demonstrated with an echocardiogram with bubble study.

162. The answer is D.

(Chap. 47) This patient has a classic presentation of thromboangiitis obliterans, or Buerger disease. This is an inflammatory occlusive vascular disorder involving small- and medium-size arteries and veins in the distal upper and lower extremities. Cerebral, visceral, and coronary vessels may be affected rarely. This disorder develops most frequently in men <40 years of age who are smokers. The prevalence is higher in Asians and individuals of Eastern European descent. Although the cause of thromboangiitis obliterans is not known, there is a definite relationship to cigarette smoking in patients with this disorder. The clinical features of thromboangiitis obliterans often include a triad of claudication of the affected extremity, Raynaud phenomenon (per Figure 24), and migratory superficial vein thrombophlebitis. Claudication usually is confined to the calves and feet or the forearms and hands because this disorder primarily affects distal vessels. There is no specific treatment except abstention from tobacco. The prognosis is worse in individuals who continue to smoke, but results are discouraging even in those who stop smoking. Arterial bypass of the larger vessels may be used in selected instances, as well as local debridement, depending on the symptoms and severity of ischemia. Antibiotics may be useful when infection is present. Anticoagulants and glucocorticoids are not helpful. Cilostazol is a phosphodiesterase inhibitor used for intermittent claudication but has no proven role in thromboangiitis obliterans. In some cases of advanced disease, amputation may be required.

163. The answer is B.

(Chap. 48) Varicose veins are dilated, bulging, tortuous superficial veins, measuring at least 3 mm in diameter. The estimated prevalence of varicose veins in the United States is approximately 15% in men and 30% in women.

Chronic venous insufficiency is a consequence of incompetent veins in which there is venous hypertension and extravasation of fluid and blood elements into the tissue of the limb. It may occur in patients with varicose veins but usually is caused by disease in the deep veins. Chronic venous insufficiency with edema affects approximately 7.5% of men and 5% of women, and the prevalence increases with age, ranging from 2% among those less than 50 years old to 10% of those 70 years old. Approximately 20% of patients with chronic venous insufficiency develop venous ulcers.

164. The answer is B.

(Chap. 48) Veins in the extremities can be broadly classified as either superficial or deep. The superficial veins are located between the skin and deep fascia. In the legs, these include the great and small saphenous veins and their tributaries. The great saphenous vein is the longest vein in the body. It originates on the medial side of the foot and ascends anterior to the medial malleolus and then along the medial side of the calf and thigh, and drains into the common femoral vein. The deep veins of the leg accompany the major arteries. There are usually paired peroneal, anterior tibial, and posterior tibial veins in the calf, which converge to form the popliteal vein. The popliteal vein ascends in the thigh as the femoral vein. The confluence of the femoral vein and deep femoral vein forms the common femoral vein, which ascends in the pelvis as the external iliac and then common iliac vein, which converges with the contralateral common iliac vein at the inferior vena cava. In the arms, the superficial veins include the basilic, cephalic, and median cubital veins and their tributaries. The deep veins of the arms accompany the major arteries and include the radial, ulnar, brachial, axillary, and subclavian veins. The subclavian vein converges with the internal jugular vein to form the brachiocephalic vein, which joins the contralateral brachiocephalic vein to form the superior vena cava. Bicuspid valves are present throughout the venous system to direct the flow of venous blood centrally.

165. The answer is C.

(Chap. 48) This is a classic clinical picture for a chronic venous insufficiency with an active venous ulcer. Symptoms in patients with varicose veins or venous insufficiency, when they occur, include a dull ache, throbbing or heaviness, or pressure sensation in the legs typically after prolonged standing; these symptoms usually are relieved with leg elevation. Additional symptoms may include cramping, burning, pruritus, leg swelling, and skin ulceration. Edema, stasis dermatitis, and skin ulceration near the ankle may be present if there is superficial venous insufficiency and venous hypertension. Findings of deep venous insufficiency include increased leg circumference, venous varicosities, edema, and skin changes. The edema, which is usually pitting, may be confined to the ankles,

extend above the ankles to the knees, or involve the thighs in severe cases. Over time, the edema may become less pitting and more indurated. Dermatologic findings associated with venous stasis include hyperpigmentation, erythema, eczema, lipodermatosclerosis, atrophie blanche, and a phlebectasia corona. Lipodermatosclerosis is the combination of induration, hemosiderin deposition, and inflammation, and typically occurs in the lower part of the leg just above the ankle. Atrophie blanche is a white patch of scar tissue, often with focal telangiectasias and a hyperpigmented border; it usually develops near the medial malleolus. A phlebectasia corona is a fan-shaped pattern of intradermal veins near the ankle or on the foot. Skin ulceration may occur near the medial and lateral malleoli. A venous ulcer is often shallow and characterized by an irregular border, a base of granulation tissue, and the presence of exudate. Ulcers due to arterial insufficiency are typically at the terminal end of a digit, since that is where flow is most limited. Diabetic ulcers are typically at pressure points such as the sides of the toes or the ball or heel of the foot. The patient's report of months of leg discomfort make *Bacillus anthracis* infection (cutaneous anthrax) and arachnid envenomation unlikely.

166. The answer is C.

(Chap. 48) Secondary lymphedema is an acquired condition that results from damage to or obstruction of previously normal lymphatic channels. Recurrent episodes of bacterial lymphangitis, usually caused by streptococci, are a very common cause of lymphedema. The most common cause of secondary lymphedema worldwide is lymphatic filariasis, affecting approximately 129 million children and adults worldwide and causing lymphedema and elephantiasis in 14 million of these affected individuals. Other infectious causes include lymphogranuloma venereum and tuberculosis. In developed countries, the most common secondary cause of lymphedema is surgical excision or irradiation of axillary and inguinal lymph nodes for treatment of cancers, such as breast, cervical, endometrial, and prostate cancer, sarcomas, and malignant melanoma. Lymphedema of the arm occurs in 13%

of breast cancer patients after axillary node dissection and in 22% after both surgery and radiotherapy. Lymphedema of the leg affects approximately 15% of patients with cancer after inguinal lymph node dissection. Tumors, such as prostate cancer and lymphoma, also can infiltrate and obstruct lymphatic vessels. Less common causes include contact dermatitis, rheumatoid arthritis, pregnancy, and self-induced or factitious lymphedema after application of tourniquets.

167. The answer is B.

(Chap. 48) Diuretics are contraindicated in patients with lymphedema and may cause depletion of intravascular volume and metabolic abnormalities. Patients should be encouraged to participate in physical activity; frequent leg elevation can reduce the amount of edema. Psychosocial support is indicated to assist patients cope with anxiety or depression related to body image, self-esteem, functional disability, and fear of limb loss. Physical therapy, including massage to facilitate lymphatic drainage, may be helpful. The type of massage used in decongestive physiotherapy for lymphedema involves mild compression of the skin of the affected extremity to dilate the lymphatic channels and enhance lymphatic motility. Multilayered, compressive bandages are applied after each massage session to reduce recurrent edema. After optimal reduction in limb volume by decongestive physiotherapy, patients can be fitted with graduated compression hose. Occasionally, intermittent pneumatic compression devices can be applied at home to facilitate reduction of the edema. Liposuction in conjunction with decongestive physiotherapy may be considered to treat lymphedema, particularly postmastectomy lymphedema. Other surgical interventions are rarely used and are often not successful in ameliorating lymphedema. Microsurgical lymphaticovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility.

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